



COMPENDIUM OF **GOOD MANUFACTURING PRACTICES (GMP)**
TECHNICAL DOCUMENTS FOR HARMONIZATION OF
MEDICINES REGULATION IN THE EAST AFRICAN COMMUNITY

VERSION SEPTEMBER 2014





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FOREWORD

This Compendium has been developed to provide guidance to National Medicines Regulatory Authorities in managing the inspection programs for Good Manufacturing Practices (GMP) of pharmaceutical manufacturing facilities.

It was compiled by the **East African Community (EAC) Technical Working Group (TWG) on GMP**. The team relied on their experiences and knowledge on pharmaceutical manufacturing including GMP requirements of their individual Countries, World Health Organization (WHO) and Pharmaceutical Inspection Cooperation Scheme (PIC/S) and other available literature.

EAC Secretariat is highly indebted to African Medicines Regulatory Harmonization (AMRH) program partners, namely WHO for their technical support; the World Bank, Bill and Melinda Gates Foundation (BMGF), the United Kingdom Department for International Development (DFID) for their financial assistance and African Union New Partnership for Africa's Development (AU-NEPAD) for high level advocacy.

In addition it is also extremely important to recognize the contribution of Clinton Health Access Initiative (CHAI) in the conceptualization stage of African Medicines Regulatory Harmonization initiative.

I wish to also thank the EAC Secretariat staff for their dedicated work and coordination of the EAC Medicines Regulatory Harmonization (MRH) Programme implementation. The oversight role of the EAC MRH Steering Committee is also acknowledged.

Finally, I would like to acknowledge regional stakeholders including the respective Ministries responsible for the EAC Affairs and Health, the EAC pharmaceutical industry and associations and the academia for their inputs in this Compendium.

Ambassador Dr. Richard Sezibera
Secretary General
EAC Secretariat



PREFACE

This Compendium has been prepared to enable effective implementation of Good Manufacturing Practices (GMP) inspection activities under the EAC Regulation Harmonization Programme. The Compendium will guide GMP inspectors in preparing for and performing GMP inspection activities of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPP). It will serve as one-stop reference on GMP.

The Compendium highlights general conditions and other pertinent requirements that are necessary for carrying out GMP inspections. It is divided into various sections describing the types of inspections, qualifications, training and experience required for inspectors as well as code of ethics and conduct to be observed by inspectors when engaged in inspection activities.

In addition, the Compendium outlines procedures to be followed when preparing and planning for joint inspection, reporting requirements including format and classification system adopted for non-compliances observed during GMP inspection.

It is also expected that the Compendium shall help inspectors to conduct GMP inspection with integrity and diligence. The Code of Ethics and Conduct for Inspectors and confidentiality agreement for performance have also been outlined with the objective to remind inspectors on their ethical and moral obligations when engaged in GMP inspection activities.

Adherence to requirements outlined in this Compendium and the referenced complementary technical documents will enable consistent conduct of GMP inspections including uniform reporting and consequently amicable decision making that minimizes complaints from manufacturers. It is therefore anticipated that the GMP inspectors shall read this Compendium and diligently apply what has been documented.

Hon. Jesca Eriyo
Deputy Secretary General for Productive and
Social Sectors
EAC Secretariat



RESPONSIBILITY FOR IMPLEMENTATION AND LEGAL FRAMEWORK

The EAC Treaty Article 118, Chapter 21 on regional cooperation on health provides for harmonization of medicines regulation among the EAC Partner States. Therefore, this Compendium will be implemented by National Medicines Regulatory Authorities (NMRAs) in accordance with the relevant policies, laws, cooperation, guidelines, manuals and procedures existing at national and regional level.

The 9th EAC Sectoral Council of Ministers of Health has officially approved the operationalization of this Compendium among the East African Community Partner States' National Medicines Regulatory Authorities (NMRAs).

Signed on this Day of2014 by the Honourable Ministers responsible for East African Community Affairs as here-in:

.....
Amb. Amina C. Mohamed, CBS, CAV	Dr. Abdallah O. Kigoda	Hon. Léontine Nzeyimana	Hon. Valentine Rugwabiza	Hon. Shem Bageine, MP
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REPUBLIC OF KENYA	UNITED REPUBLIC OF TANZANIA	REPUBLIC OF BURUNDI	REPUBLIC OF RWANDA	REPUBLIC OF UGANDA



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PART ONE:
**INSPECTION MANUAL FOR GOOD
MANUFACTURING PRACTICE**



1. ABBREVIATIONS AND ACRONYMS

API	-	Active Pharmaceutical Ingredient
AU-NEPAD	-	African Union New Partnership for Africa's Development
EAC	-	East Africa Community
FPP	-	Finished Pharmaceutical Product
GMP	-	Good Manufacturing Practices
MRH	-	Medicines Regulation Harmonization
NMRA	-	National Medicines Regulatory Authority
PIC/S	-	Pharmaceutical Inspection Cooperation Scheme
SOP	-	Standard Operating Procedure
TWG	-	Technical Working Group
WHO	-	World Health Organization



2. GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Conflict of interest means any interest in any business related to medicines declared by GMP inspector that may affect or reasonably perceived to affect the quality or the result of his/her work or remediation.

Critical observation means an observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

GMP Inspector means a GMP Inspector is an officer appointed by the NMRA of a Partner State in accordance with national regulations and the provisions of the NMRA to conduct an inspection or assessment in order to verify GMP compliance of a manufacturing site on behalf of the NMRA.

Lead GMP Inspector is a Senior GMP Inspector who is charged with the responsibility for leading a GMP inspection team to undertake inspection of a specified pharmaceutical manufacturing site(s).

Major observation means an observation describing a situation that may have an impact on the product but is not as significant as a critical observation. It may have an indirect impact in the strength, identity, purity or safety of the product. There is reduced usability of the product without a probability of causing harm to the consumer. Observation of a major deficiency puts a question mark on the reliability of the firm's quality assurance system.

Minor observation means an observation describing a situation that is a departure from GMP but has no significant impact on the product quality. It has low probability of affecting the quality or usability of the product.

Re-qualification implies validation of the GMP inspector after 24 months absence from conducting GMP inspections to ensure the officer possesses the knowledge and skills to carry out GMP inspections

Senior GMP Inspector is an officer who by virtue of experience and competence is appointed as such to conduct GMP inspections and train junior officers in inspections after evaluation by the NMRA as by the criteria outlined in the assessment form.

Specialized GMP Inspector is a GMP inspector who possesses specialized knowledge and experience in conducting GMP inspections for specialized areas e.g. Microbiology, HVAC, Biologicals, API, e.t.c.



3. INTRODUCTION

The EAC-MRH Programme was established to improve public health through harmonization of medicines regulation and all matters related to improved access to medicines of acceptable quality, efficacy and safety in the EAC region.

Regulation of medicinal products involves among other things, inspection of pharmaceutical plants to verify compliance to GMP. GMP is that part of quality assurance which ensures that products are consistently produced and controlled to meet quality standards appropriate for the intended use and as required by marketing authorization. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

GMP inspections are conducted as one of the requirements for registration of medicinal products in the EAC. Such inspections are also conducted for operating as well as new pharmaceutical plants so as to verify compliance with GMP standards. Inspection involves review of documents, records, facilities and any other resources to assess their conformity to the requirements of EAC GMP of medicinal products.

Consistency in conducting GMP inspection activities is very important in ensuring quality assurance of pharmaceuticals by the NMRA. This results into common decision making by different EAC GMP inspectors at the end of inspections and thus avoiding complaints from manufacturers.

In order to achieve that goal, EAC GMP inspectors need to be provided with this Manual which contains sufficient working tools needed for observing, investigating and reaching conclusions in a particular inspection.

The Manual highlights general conditions and other pertinent requirements that are necessary for carrying out GMP inspections. It is divided into various sections which amongst other things outline different types of inspections, qualifications, training and experience required for inspectors as well as code of ethics and conduct to be observed by inspectors when engaged in inspection activities. Moreover, the Manual defines procedures to be followed when preparing and planning for inspection, reporting requirements including format and classification system adopted for non-compliances observed during GMP inspection.

Various working documents are also referred to in this Manual to help inspectors to comprehend matters related to GMP. It is also expected that the Manual shall help inspectors to conduct GMP inspection with integrity and diligence.

4. SCOPE

The Manual is applicable for all types of GMP inspections for pharmaceutical manufacturing plants of API and FPP in the EAC Partner States NMRAs. This Manual serves as a guide to EAC GMP inspectors in preparing for and performing GMP inspection activities. It also serves as reference document for inspectors prior and during GMP inspection.



5. TYPES OF INSPECTIONS

There are four types of inspection as indicated below;

- a) Routine inspection
- b) Concise inspection
- c) Follow-up inspection
- d) Special inspection

5.1. ROUTINE INSPECTION

Routine inspection is a full review of all aspects and components of GMP within a facility. Routine inspection is conducted under the following circumstances:

- a) To a newly established manufacturing facility or a manufacturer who has expressed interest of expanding manufacturing activities e.g. introduction of new products.
- b) When there is modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment.
- c) When GMP certification has expired.

This type of inspection should be announced.

5.2. CONCISE INSPECTION

Concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. A limited number of GMP requirements are selected by the inspector to serve as indicators of the overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection.

Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude toward GMP.

A concise inspection is conducted under the following circumstances:

- a) Where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past.
- b) Where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection. These inspections can be announced or unannounced.

5.3. FOLLOW-UP INSPECTION

A follow up inspection is also referred to as a re-inspection or a reassessment of the manufacturing facilities. It is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection. Depending on the nature of the defects and the work required, the follow-up inspection could be carried out within the agreed timeframe after the previous inspection.

The follow-up inspection is limited to specified GMP non compliances that have been observed. A follow up inspection shall be unannounced.



5.4. SPECIAL INSPECTION

A special inspection is undertaken to do spot checks which could focus on one product, a group of related products, or specific operations e.g. mixing, or labeling.

Special inspection is conducted under the following circumstances:

- a) When there are complaints about a specific product that suggest there may be defects.
- b) When there is a product recall due to events such as adverse drug reactions.
- c) To gather specific information, or to investigate specific operations of the manufacturing processes.

The inspection shall be unannounced.

6. FREQUENCY OF INSPECTIONS

The frequency of inspection of local and foreign manufacturers shall be as follows:

6.1 LOCAL PHARMACEUTICAL MANUFACTURERS

Local manufacturers shall be inspected once a year or after 2 years depending on the type of inspection to be performed.

6.2 FOREIGN PHARMACEUTICAL MANUFACTURERS

Foreign manufacturers shall be inspected once after 3 years. A manufacturer may be inspected more than once within 3 years, depending on the type of inspection to be performed.

7. PLANNING FOR GMP INSPECTIONS

The planning for GMP inspection shall be as per EAC Procedure for Planning for GMP Inspections (EAC/TF-MED/GMP/FD/SOP/N1R0).

While planning for GMP inspection, the following categories of manufacturers should be considered;

a) Facilities located within the EAC Region

All applicants with their own and contracted manufacturing sites shall be inspected at regular intervals in accordance with the EAC NMRAs recommendation - at least annually for routine GMP inspection.

b) Facilities located in foreign countries

All facilities located in countries outside the EAC region shall be subject to GMP Inspection once every three years unless otherwise notified. Facilities located in countries with stringent NMRAs shall be subject to a first inspection and thereafter may be assessed using document review unless otherwise required.



c) Manufacturers of APIs

Manufacturers of APIs shall be inspected on a risk-based basis. For the purpose of this Manual, high risk categories shall include, but not be limited, to the following:

- i. Manufacturers of sterile APIs who do not have approval of stringent regulatory authorities.
- ii. Manufacturers of APIs for anti-retroviral, anti-malarial and anti-tuberculosis medicinal products who do not have approval of stringent regulatory authorities.
- iii. Manufacturers of relatively unstable APIs who do not have approval of stringent regulatory authorities.
- iv. Manufacturers of APIs for which market complaints have been received

8. PREPARATION FOR GMP INSPECTION

The preparation for GMP inspection shall be as per the EAC **Model Procedure for Preparation for GMP Inspection (EAC/TF-MED/GMP/FD/SOP/N2R0)**.

9. JOINT GMP INSPECTION

GMP inspection within the EAC shall be conducted as per the EAC **Model Procedure on Conducting Joint GMP Inspection (EAC/TF-MED/GMP/FD/SOP/N4R0)**.

10. QUALIFICATION OF GMP INSPECTOR

EAC NMRAs shall appoint inspectors to inspect domestic and overseas manufacturing facilities where medicines used in EAC are manufactured. GMP inspectors should have the necessary qualification in order to effectively take part in inspection of pharmaceutical manufacturing facilities. The qualification of GMP inspectors should be in line with the EAC **Guidelines on Training and Qualification of GMP Inspectors (EAC/TF-MED/GMP/FD/GDL/N3R0)**.

11. CODE OF ETHICS AND CONDUCT FOR GMP INSPECTORS

The code of ethics and conduct for GMP inspectors should be in line with the EAC **Code of Ethics and Conduct for GMP Inspectors (EAC/TF-MED/QMS/FD/POL/N2R0)**.

12. DECLARATION OF CONFLICT OF INTERESTS

The declaration of conflict of interests should be done as per the EAC **Code of Ethics and Conduct for GMP Inspectors (EAC/TF-MED/QMS/FD/POL/N2R0)**.

13. CONDUCTING GMP INSPECTION

GMP inspection shall be conducted as per the EAC **Model Procedure for Conducting GMP Inspection (EAC/TF-MED/GMP/FD/SOP/N3R0)**.



14. SAMPLE COLLECTION AND TESTING

The inspection may include the collection of samples for verification of quality parameter as deemed necessary by the inspectors as per the **Model Procedure for Sample Collection and Handling (EAC/TF-MED/GMP/FD/SOP/N5R0)**. Normally, the sample size should be sufficient to carry out the test for investigated parameter(s). Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

- a) tablets and capsules: 100 units per batch;
- b) injections (single component): 20 units per batch;
- c) injections (combination): 20 units per batch;
- d) oral powders for reconstitution: 10 units per batch;
- e) liquid formulations: 5 bottles/units per batch.

15. INSPECTION REPORT

Inspection report should be written immediately after completing the inspection. The compiled report shall be shared within the NMRA and members of the EAC GMP TWG within fourteen (14) calendar days upon completion of inspection. The EAC GMP TWG shall make sure that GMP inspection report is sent to the inspected facility within thirty (30) calendar days after receiving the inspection report.

GMP inspection report shall be written according to the EAC **Model Procedure for Preparing and Reviewing GMP Inspection Report (EAC/TF-MED/GMP/FD/SOP/N6R0)**. Sufficient details should be provided to allow for an independent assessment, comprehension and easy decision making.

Observations made that are considered to be non-compliance with EAC GMP requirements should be listed and cross referenced. Where observations are included in the report, clear distinction should be made between “compliances” and “non-compliances”. Non-compliance observations should be classified as “critical”, “major” and “minor”. These classes are detailed below.

16. CLASSIFICATION OF GMP INSPECTION OBSERVATIONS

The intention of this part is to help classify the non-compliances observed during GMP inspection. Overall, the evaluation should commensurate with the nature and extent of the deviations (i.e. severity). Situations involving fraud, misrepresentation or falsification of source data or records linked with pharmaceutical manufacturing will result in a non-compliance rating.

Non-compliances should be noted by Inspectors and classified as critical, major and minor (refer to the EAC **Model Procedure for Risk Classification of GMP Deficiencies (EAC/TF-MED/GMP/FD/SOP/N7R0)**).



17. RECOMMENDED REGULATORY ACTION(S)

Below is a table showing a set of regulatory actions that can be recommended by inspectors when making decisions on the outcome of inspections.

S/N	Category of non-compliances	Regulatory action(s)
1.	Minor	<ul style="list-style-type: none">• Recommend corrective action within a given timeframe• Request for compliance report
2.	Major	<ul style="list-style-type: none">• Issue warning letter• Recommend corrective action within a given timeframe• Recommend temporary withdrawal or suspension of marketing authorization• Request for comprehensive compliance report• Follow-up inspection to verify implementation if necessary
1.	Critical	<ul style="list-style-type: none">• Recommend permanent withdrawal of marketing authorization in case of registered products• Recommend suspension of marketing authorization in case of registered products• Recommend not to grant marketing authorization for new application.

Please refer to the **Model Procedure for Follow Up on Non-Compliances After GMP Inspection (EAC/TF-MED/GMP/FD/SOP/N7R0)**.



18. PRODUCT RECALL

The product recalls should be conducted as per the **Model Procedure on Handling Product Recalls (EAC/TF-MED/GMP/FD/SOP/N9R0)**.

19. APPEAL

Any manufacturer may appeal against any decision of the NMRA.

When a manufacturer appeals against a decision of NMRA, the written submission by the manufacturer will be evaluated by the NMRA. The NMRA will then decide whether to accede to the appeal of the manufacturer after evaluating the submitted reason (s) appeal. The NMRA may consider the reason (s) and motivation for appeal and accept or reject the appeal according to the national and regional regulations.

20. REFERENCES

- a) WHO Prequalification Programme documents:
<http://apps.who.int/prequal/>
- b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance documents on inspection: www.picscheme.org
- c) EAC Partner State guidelines and SOPs on GMP inspection



21. REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	17th April 2014	EAC TWG GMP Members	All	First approved version to be issued	REF: EAC/ SC...../ DECISION 17TH APRIL 2014

22. LIST OF COMPLEMENTARY DOCUMENTS

- a) Code of Conduct for EAC NMRAs (**EAC/TF-MED/QMS/FD/POL/N2R0**) in PART V of the Compendium on Quality Management System (QMS)
- b) Guidelines on Good Manufacturing Practice for Medicinal Products for Use in EAC (**EAC/TF-MED/GMP/FD/GDL/N1R0**) in PART TWO of the Compendium on Good Manufacturing Practices (GMP)
- c) Guidelines on Preparation of Site Master File for Pharmaceutical Manufacturing Facilities (**EAC/TF-MED/GMP/FD/GDL/N2R0**) in PART THREE of the Compendium on Good Manufacturing Practices (GMP)
- d) Guidelines on Training and Qualifications of GMP Inspectors (**EAC/TF-MED/GMP/FD/GDL/N3R0**) in PART FOUR of the Compendium on Good Manufacturing Practices (GMP)
- e) Model Procedure for Planning for GMP Inspections (**EAC/TF-MED/GMP/FD/SOP/N1R0**) - Annex 1
- f) Model Procedure for Preparation for GMP Inspection (**EAC/TF-MED/GMP/FD/SOP/N2R0**) - Annex 2
- g) Model Procedure for Conducting GMP Inspections (**EAC/TF-MED/GMP/FD/SOP/N3R0**) - Annex 3
- h) Model Procedure for Conducting Joint GMP Inspections (**EAC/TF-MED/GMP/FD/SOP/N4R0**) - Annex 4
- i) Model Procedure for Sample Collection and Handling (**EAC/TF-MED/GMP/FD/SOP/N5R0**) - Annex 5
- j) Model Procedure for Preparing and Reviewing of GMP Inspection Reports (**EAC/TF-MED/GMP/FD/SOP/N6R0**) - Annex 6
- k) Model Procedure for Risk Classification of GMP Deficiencies (**EAC/TF-MED/GMP/FD/SOP/N7R0**) - Annex 7
- l) Model Procedure for Follow up on Non-compliances after GMP Inspection (**EAC/TF-MED/GMP/FD/SOP/N8R0**) - Annex 8
- m) Model Procedure for Handling Product Recall (**EAC/TF-MED/GMP/FD/SOP/N9R0**) - Annex 9





ANNEX 11: MODEL PROCEDURE FOR PLANNING FOR GMP INSPECTION

1. PURPOSE

The purpose of this SOP is to ensure that GMP Inspectors follow a standardized procedure when planning for routine GMP inspections. This should assist with ensuring a consistent approach in conducting inspections.

2. SCOPE

The scope of this SOP applies for planning GMP inspections of manufacturers of FPPs and of APIs applied within the EAC Partner States, including joint GMP inspection.

3. RESPONSIBILITY

- 3.1 Head of NMRAs
- 3.2 Head GMP department
- 3.3 Lead Inspectors
- 3.4 GMP Inspectors
- 3.6 Procurement department
- 3.7 Human Resource Unit

4. DISTRIBUTION LIST

- 4.1 Head of NMRAs
- 4.2 Head of GMP departments
- 4.3 NMROs
- 4.4 Joint GMP Inspection Coordinators
- 4.5 Quality assurance departments

5. PROCEDURES

5.1 Selection of Companies to be Inspected

- 5.1.1 Selection of facilities to be inspected is considered an initial and crucial step in planning for an inspection.
- 5.1.2 The concerned department shall undertake the selection and ensure that:
 - 5.1.2.1 The local technical representative or manufacturer should have filled in the details of the inspection on a form with details of actual site to be inspected, lines and contact details of the responsible persons.
 - 5.1.2.2 The local technical representative/ manufacturer will also have to pay the prescribed fee for the GMP inspection
 - 5.1.2.3 Selection shall ideally be based on first application first inspected basis.
- 5.1.3 Without unduly contravening the provision 5.1.5 above, facilities may be selected based on;
 - 5.1.3.1 Type of activities/products; Sterile/Non sterile products, Biological/biotechnological products, Packaging or API production
 - 5.1.3.2 Need to expedite an ongoing regulatory decision process
 - 5.1.3.3 Public health/interest; Need to meet a health emergency in the country
- Others



- 5.1.3.4 Prevailing Socio-political atmosphere
- 5.1.3.5 Economic/cost effectiveness of conducting the inspections
- 5.1.3.6 Weather/climatic
- 5.1.3.7 Availability of inspectors with specialized expertise in the team
- 5.1.3.8 Level of compliance in the previous inspection (Type/class of findings in the previous inspection, Criminal/illegal practices)
- 5.1.3.9 Expiry of compliance certification
- 5.1.3.10 Type of inspection to be carried out (refer to Types of inspection).

5.2 Scheduling of Selected Companies for Inspection

- 5.2.1 Allocation of dates and durations of inspection shall be made based on;
 - 5.2.1.1 Type of inspection to be performed and the purpose of the inspection or visit.
 - 5.2.1.2 Anticipated duration of inspection based on plant size, number of blocks/production lines and activities
 - 5.2.1.3 A combination of all, or some of the factors for selection as appropriate.
- 5.2.2 Scheduling to be carried out within a period of six months and allocate tentative dates and will be checked and reviewed regularly within the specified period.

- 5.2.3 The Head of the GMP Inspectorate department shall appoint the inspection team and designate the lead inspector with the adequate competency as per the inspection to be undertaken.

5.3 Out-of-Site Planning for the Inspection

Once the inspection is allocated to a dully-constituted inspection team, the GMP Unit shall be responsible for planning for the performance of the inspection as follows:

- 5.3.1 Inform the manufacturer(s) through the respective local agents of the proposed date(s) for the inspection and organize letter for invitation to assist in the preparation for travel.
- 5.3.2 Ensure that the proposed dates for the inspections are suitable for members of the inspection team.
- 5.3.3 Appropriately fill Form 1 for the necessary information that will be used to organize the inspection and facilitate approval.
- 5.3.4 Verify the objective of the inspection that is to be carried out.
- 5.3.5 Determine what the scope and depth of the inspection will be to enable to prepare properly for the inspection.
- 5.3.6 Scrutinize the relevant documents as indicated in SOP for Preparing for inspection.



5.4 Dossier Submission

The dossiers have to be submitted before GMP application and inspection should be carried out before issuing the Marketing authorization.

5.5 Re-Inspection

The CAPA and/or previous GMP inspection reports should be reviewed before planning for the GMP inspection.

5.6 Administration

5.3.7 Inform the administration to organize logistics for inspectors

6.0 REFERENCES

WHO PQP SOP; PLANNING FOR AN INSPECTION

7.0 REVISION HISTORY

Name	NMRA	Contact (emails & Tel)



1. PARTICULARS OF APPLICANT/LICENSE HOLDER

Name_____

Physical Address_____

Country_____ Telephone_____

Fax_____ E-mail_____

2. PARTICULARS OF SITE TO BE INSPECTED

Name of site_____

Physical Address (if different from 1. above)

Country_____ Tel_____

Fax_____ E-mail:_____

Note: Separate application to be filled in for each individual site

3. CONTACT PERSON ON SITE

Name of contact person_____

Tel: _____ Fax: _____

E-mail: _____

4. AUTHORISED REPRESENTATIVE/AGENT IN THE COUNTRY

Name of Local Technical Representative_____

Tel: _____

5. TYPE OF MEDICINES

Type of medicines manufactured *(Tick where applicable)*

(a) Human (b) Veterinary (c) Both (a) and (b)

6. REGISTRATION OF PRODUCTS

Have you registered any products in the country YES NO

Have you submitted dossier for registration? YES NO

If YES, list the products applicable. *(Attach a separate sheet if needed)*

.....



7. PRODUCTION LINES TO BE INSPECTED

DOSAGE FORM	Tick where applicable	*CATEGORY	**ACTIVITIES
Tablets			
Capsules			
Injections (SVP)			
Injections (LVP)			
Oral liquids			
Creams/Ointments/lotions			
Others (specify)			

* Category means any of the following;
 Beta lactam, Non-beta lactam, Biologicals, Vaccines, Hormones, Cytotoxic products

- ** Activity means any of the following:
- Formulation(dispensing, mixing, blending)
 - Processing(compression, emulsification etc)
 - Packing
 - Quality Control
 - Warehousing(raw material, finished products)

8 DECLARATION

Commitment from manufacturers to welcome inspectors for inspection any time
 I hereby certify that the above information is correct and apply for Good Manufacturing Practice inspection of the above-named site(s).

Signature of applicant..... Date.....
 Print Name.....

Notes:

1. Please submit a copy of the Site Master File (not more than 25 pages) together with this application (refer to Guideline on preparation of a Site Master File)
2. This application must be submitted together with the appropriate fee to the Head of NMRA



FOR OFFICIAL USE ONLY:

INSPECTION TYPE *(Please tick where applicable)*

- First Inspection
- Routine Re - inspection
- Joint Inspection
- Other (please specify).....
- Re - inspection after failure
Previous inspection date.....

OFFICER ASSIGNED FOR INSPECTION

Name of the Officers:

Name	NMRA	Contact (emails & Tel)



ANNEX 12: MODEL PROCEDURE FOR PREPARING FOR GMP INSPECTION

1. PURPOSE

The purpose of this SOP is to ensure that a standardized procedure is followed by all inspectors when preparing for routine inspections in order to ensure a consistent approach in conducting inspections.

2. SCOPE

The scope of this SOP applies for preparation of GMP inspections of manufacturers of FPPs and of APIs applied within the EAC Partner States, including joint GMP inspection.

3. RESPONSIBILITY

3.5 Head of NMRAs

3.6 Head GMP department

3.7 Lead Inspectors

3.8 GMP inspectors

4. DISTRIBUTION LIST

4.1 Head of NMRAs

4.2 Head of GMP departments

4.3 NMROs

4.4 Joint GMP Inspection Coordinators

4.5 Quality assurance departments

5. PROCEDURE

5.1. Inspectors should properly prepare for inspections, including familiarization with products, sites, types of technologies.

5.2 Once the inspection is allocated to the inspection team, the Lead Inspector is responsible for planning for the performance of the inspection as follows:

5.2.1 Inform the relevant people meant to prepare the relevant documents at least 14 days before inspection.

5.2.2 Verify the objective of the inspection that is to be carried out.

5.2.3 Verify whether the inspection will cover the entire factory or just part of it.

5.2.4 Determine what the scope and depth of the inspection will be to prepare properly for the inspection.

5.2.5 Scrutinize the product dossiers for the products manufactured in the respective manufacturing site.

5.2.6 Decide what products will be covered during the inspection.

5.2.7 Review assessment reports from the dossier for individual products including assessment remarks.

5.2.8 Liaise with relevant departments/officers for any specific information related to the selected;

5.2.8.1 **Pharmacovigilance and post market surveillance reports.**

5.2.8.2 **Product dossiers and any notification/ Amendments**

5.2.8.3 **Previous inspection reports/CAPAs, if available**



5.2.9 Confirm the amount of time that will be required to carry out the inspection and plan the date when the inspection will take place.

A routine inspection for one site can be performed over a period of at least two to five working days. The length of an inspection is determined by a number of factors, including the type of inspection to be performed, the number of inspectors, the size of the company and the purpose of the inspection or visit. Annex: criteria for deciding the duration.

5.2.9 Study the Site Master File and make notes to be followed up during the inspection (e.g. available equipment, SOPs, records). Study the layout and design of the facility to get a better understanding of the flow of material, personnel and processes in the facility. Study some of the systems the organization has in place (e.g. HVAC and Water).

5.2.10 If a current SMF does not exist, request for an updated copy from the company.

5.2.11 If desired, prepare a checklist of points to be verified during the inspection. Prepare notes for verification in the aide memoire specific to site to be verified during the inspection.

5.2.12 Prepare a Tentative Inspection Plan (Annex I) which can be used as a template that can be modified. Indicate in the programme which sections or departments will be inspected, and when.

5.2.13 Distribute the Plan to the team members for comments and after finalization, to the company approximately 2 weeks before the inspection.

5.4 Re-Inspection

5.4.1 During preparation for GMP inspection, the CAPA and/or previous GMP inspection reports should be reviewed.

6. REFERENCE

WHO PQP SOP 402.1;
PREPARING FOR AN INSPECTION

7. REVISION HISTORY

SOP VERSION	DATE AUTHORISED	REASON FOR CHANGE	AUTHORISED BY



Manufacturer:	
Address:	
Date:	
Reference:	
Inspector(s):	

TIMESFORGUIDANCEONLY

Day1-AM	
OPENING MEETING 8.30AM	Introductions
	Objectives and scope of the inspection
	Confirmation of the proposed programme
	Brief presentation of the factory
	Recent changes
DOCUMENT REVIEW	Quality system
	QM and quality policy
	Validation Master Plan
	Change control and deviation management: SOP's+ summary list of changes and deviations (2010-2011)
	Annual product review for above mentioned products
	Risk management
	Complaints: SOP+ summary list of complaints of(2010-2011)
	Recalls: SOP + summary list of recalls of (2010-2011)
	Site plan, production block layout, indicating the HVAC system and AHU's, material and personnel flow
	HVAC system schematic drawing and summary of specifications for HVAC
	Purified water system plan and summary of specifications for PW
	Compressed air system schematic drawing and summary of specifications for compressed air
	Day1-PM
SITEINSPECTION	Receiving area and stores



	Starting materials, packaging materials and components
	Finished products
	Sampling, dispensing and issuing
DAY2-AM	
CONTINUATION OF SITE INSPECTION	Production of tablets-following material flow
Day2-PM	
INSPECTION OF PRODUCTION ACTIVITIES	Production of tablets-continuation Utilities <ul style="list-style-type: none">• HVAC system• PW system• Compressed air system

Day3-AM	
LABORATORY INSPECTION	Wet chemistry laboratory
	Instrumental laboratory
	Laboratory materials management
	Microbiological laboratory
	Retention samples storage
Day3-PM	
DOCUMENTSREVIEW	Review of remaining documents
CLOSING MEETING	Approximately4.30pm

Notes:

- Tea and lunch breaks will be taken at suitable times
- The inspection will start at approx. 8.30am and finish at approximately 5pm each day
- At the end of each day if need be a brief meeting will be held to review the findings and discuss the plan for the next day



ANNEX 13: MODEL PROCEDURE FOR CONDUCTING GMP INSPECTION

1. PURPOSE

The purpose of this SOP is to ensure that all inspectors when performing inspections follow a standardized procedure and to ensure consistency in performance between different inspectors.

2. SCOPE

The scope of this SOP applies to conducting GMP inspections for manufacturers of FPPs and of APIs applied within the EAC Partner States, including joint GMP inspection.

3. RESPONSIBILITY

3.1 Head of NMRAs

3.2 Head GMP department

3.3 Lead Inspectors

3.4 GMP inspectors

4. DISTRIBUTION LIST

4.1 Head of NMRAs

4.2 Head of GMP departments

4.3 NMROs

4.4 Joint GMP Inspection Coordinators

4.5 Quality assurance departments

5. PROCEDURES

5.1 The Inspectors should identify themselves at the entrance of the site before entering the site

5.2 All inspections should be started with an opening meeting. See form number EAC/TF-MED/GMP/FD/FOM/N3R0 for guidance on what should be covered during the meeting.

5.3 Confirm the inspection plan to the company and refer to the standard(s) against which the inspection will be done.

5.4 Circulate the attendance record form EAC/TF-MED/GMP/FD/FOM/N4R0 to enable all persons present to record names, positions in the company and email address.

5.5 Conduct the inspection through assessment of compliance with GMP according to the inspection plan. Adjust the inspection plan if necessary.

5.6 During routine inspections all aspects described in the GMP guidelines should be assessed as far as possible. Emphasis should be placed on specific areas based on a risk approach and time allocated accordingly.

5.7 Verify selected source data where possible. This is done by requesting documentation, records and raw data. It may be helpful to make a list of documents requested to ensure that all requested are provided and reviewed. See form **EAC/TF-MED/GMP/FD/FOM/N5R0**.

5.8 Maintain notes during the inspection and keep this record for filing on the company files after completion of the inspection.



5.9 Observations should be discussed with the company representatives at the time that they are noted.

5.10 In addition provide feedback to the company/laboratory / organization on the observations (deficiencies) made during the inspection. This should normally be done at the end of each day. No deficiencies should be included in the report if these we're not mentioned/ discussed with the company.

5.11 At the end of the inspection, arrange for a closed meeting between inspectors to discuss the deficiencies in preparation for the closing meeting.

5.12. End the inspection with a closing meeting where the lead inspector should summarize the findings with the representatives of the company. The importance of the deficiencies should be mentioned. See form **EAC/TF-MED/GMP/FD/FOM/N3R0** for guidance on what should be covered during the meeting.

5.13 At any stage during the inspection, if serious deficiencies are

observed that may lead to possible serious risk to patients, the Lead Inspector should immediately contact the Head, Regulatory body and Head of GMP Inspectorate (as appropriate for each country) to decide what action should be taken. The company should be so informed.

6. RECORDKEEPING

6.1. The inspection plan, meeting attendance record, notes made during the inspection, any checklists used, record of documents requested (if used), copies of any documents requested during the inspection, should be filed on the company file after the inspection report has been prepared and sent to the company. See form **EAC/TF-MED/GMP/FD/FOM/N5R0**

6.2. All documents mentioned in the section 6.1.should be filed in the company file by the relevant secretary who arranged the inspection.

7. REFERENCE

WHO PQP Sop 403.1; Conducting an Inspection

8. REVISION HISTORY

SOP VERSION	DATE AUTHORISED	REASON FOR CHANGE	AUTHORISED BY



9.0 ANNEXES

Annex1: Guidance points for opening and closing meeting

Annex II: Record of persons present in the opening and closing meeting

Annex III: Record of documents requested during an inspection (optional)

OPENING MEETING

Opening the meeting should at least include but not limited to the following;

- i. Introduction of the inspectors
- ii. Ask the company to introduce the people present and to make a brief presentation
- iii. Explain how the inspection is to be conducted
- iv. Scope of the inspection
- v. Inspection plan
- vi. Discuss Inspection Time Table
- vii. How the feedback will be given e.g. end of each day
- viii. Which are the standards that will be applied(EAC- GMP)

CLOSING MEETING

- i. Thank the company for their cooperation

- ii. Provide brief feedback on some of the positive points noted in the inspection
- iii. Explain the process and time lines for the report and corrective action plan
- iv. Explain that the closing meeting allows providing a summary of the observations made-and the intention is not to list each observation

(Note: You should have discussed the observations made at the end of each day or at some point during the inspection. No surprises in the inspection report!)

- v. Provide a summary of issues of concern under different areas such as:
 - Quality Assurance
 - Documentation
 - Personnel
 - Premises
 - Equipment
 - Materials
 - Cleaning/sanitation/Hygiene
 - Production
 - Quality control
 - Validation
 - Utilities
- vi. Mention ,if relevant, whether there are any critical or major deficiencies
- vii. Ask if the company needs clarification on any point



Manufacturer:	Address:
Inspector(s):	
Opening meeting Date:	Closing meeting Date:

To be completed by representatives of the manufacturer:

Name (please print)	Position in the organization	E-mail address	Signature



Manufacturer:

Inspector:

Date:

Sr No	Document	Docum ent no.	Time request	Time nresent
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ANNEX 14: MODEL PROCEDURE FOR CONDUCTING JOINT GMP INSPECTION

1. PURPOSE

The purpose is to outline procedures for EAC NMRAs participating in joint GMP inspections program, taking into account risk based approaches, building on similar GMP standards and mutual confidence and agreement between regulatory authorities.

2. SCOPE

The scope of this procedure includes EAC joint GMP inspections of manufacturers of FPPs and of APIs, which are of common interest to two or more EAC NMRAs. I

t is recommended for both pre- and post-approval inspections.

3. RESPONSIBILITY

3.1 Head of NMRAs to allocate adequate resources

3.2 Head GMP department:

3.2.1 Ensuring that administrative or enforcement actions at national/ regional level are undertaken as appropriate e.g. database entry, issuance/update of certificates/ licenses

3.2.2 Act as a contact person at the NMRA and to share any information relevant to joint EAC NMRAs inspections.

3.2.3 Appoints and assigns inspectors, or lead inspector if required, to a joint EAC NMRAs inspections

3.3 The lead inspector has the following duties:

3.3.1 Setting a reporting deadline in agreement with all team members taking into account any specific deadlines linked to on-going submissions/applications or procedures;

3.3.2 Technical preparation of the inspection with the inspected facility representative and in liaison with the other inspectors of the team

3.3.3 Establishing a draft inspection plan in cooperation with the involved regulators and arranging for a pre-inspectional preparation meeting;

3.3.4 Leading the conduct of the inspection on site;

3.3.5 Communication between the representative of inspected facility and the inspection team;

3.3.6 Facilitate the discussion for all the findings/observations jointly agreed with the inspection team

4. DISTRIBUTION LIST

4.1 Head of NMRAs

4.2 Head of GMP departments

4.3 NMROs

4.4 Joint GMP Inspection Coordinators

4.5 Quality assurance departments



5. PROCEDURE

5.1 GENERALS

5.1.1 For this procedure, general principles and terms of reference agreement EAC/TF-MED/GMP/FD/FOM/N6R0 shall apply as necessary.

5.1.2 All the NMRAs within the EAC identify a Joint inspection coordination within its ranks specifically for joint inspection coordination purposes; preferably head of the GMP Department.

5.1.3 For the purpose of collaboration and communication, a joint inspection coordination committee should be created with the Joint GMP Inspection coordinators as primary members.

5.2 INITIATION OF A JOINT INSPECTION

5.2.1 A joint inspection can initiate through three mechanisms such as:

- a) An official request from a manufacturer
- b) A joint interest of at least two EAC NMRAs
- c) A joint procedure in the framework of a multiple application for marketing authorization to more than one EAC NMRAs.

Case a)

5.2.2 Companies requiring either pre- or post-registration/approval inspections from any two or more

EAC NMRAs may contact the concerned EAC NMRAs to express interest in a joint inspection. The request should be submitted in the prescribed format, adding in the comments the countries/NMRAs involved.

5.2.2.1 Requests for participation in the EAC Partner States joint inspections should be sent by the requesting applicant to the EAC NMRAs so that the evaluation of the request can be efficiently performed by the NMRAs and any required documentation provided. **See Clause 2.11 of document number EAC/TF-MED/GMP/FD/FOM/N6R0**

5.2.2.2 Applicants should address one single "Request for joint inspection" letter to the concerned NMRAs. In this letter, the applicant should provide countries of interest together with details of the product, manufacturing site, manufacturing process, inspection history of the manufacturer and all other information considered relevant. **See Clause 2.12 of document number EAC/TF-MED/GMP/FD/FOM/N6R0**

5.2.2.3 In addition, the applicant should explicitly authorize in the request the comprehensive exchange between the NMRAs of all information relevant to the subject. **See Clause 2.13 of document number EAC/TF-MED/GMP/FD/FOM/N6R0**



Case b)

5.2.3 Alternatively, one NMRA can submit the interest to its counterparts to organize a joint inspection. If this suggestion is agreed among two or more NMRAs, they can seek a written “no objection” for a joint EAC- GMP Inspections to the companies they share interest on.

Case c)

5.2.4 Finally, in the framework of multiple applications sent to several EAC NMRAs, the manufacturer acknowledges the possibility to be inspected by a joint team of EAC inspectors. The applicant should explicitly authorize in the application the comprehensive exchange between the NMRAs of all information relevant to the subject.

5.3 DECISION REGARDING THE PERFORMANCE OF A JOINT INSPECTION

5.3.1 The GMP NMRAs Joint Inspection coordinators shall share information on manufacturing sites that have expressed interest in participating in a joint EAC inspection.

5.3.2 The GMP Inspection coordinators shall set up a communication platform (e.g teleconference, email, skype call) to agree that a joint EAC inspection is warranted, determine timelines and identify the inspection team and lead inspector.

5.3.3 Based on the information/response received and the common areas of interest, the concerned authorities

will decide or not to perform a joint inspection in accordance with the principles and procedures outlined below.

5.3.3.1 The inspection coordinators will together decide who the leading inspection authority will be, taking into account the following:

For manufacturing sites in the EAC; the lead inspector will be the authority other than the country where the manufacturing site is located.

For manufacturing sites outside the EAC: the lead inspector will be allocated on a case-by-case basis taking into account: the expertise and competencies, the inspection history of the site and the number of concerned finished pharmaceutical products or active ingredients in each country. Keeping a good balance between the various NMRAs.

5.3.4 In case of a request, the decision made is forwarded to the manufacturer. If the contacted or concerned agencies agree to conduct a joint inspection, the applicant should receive an electronic mail message acknowledging such agreement. The message should state the primary contact person at each agency for the specific inspection. **See Clause 2.17 of document number EAC/TF-MED/GMP/FD/FOM/N6R0**



5.3.5 In the other cases, the letter sent in advance of the inspection will inform officially of the joint inspection.

5.4 PLANNING FOR THE JOINT INSPECTION

5.4.1 The joint inspection planned should be integrated in the planning of each NMRAs.

5.4.2 The plan of jointed inspection is updated by a chair of the coordination committee.

5.5 PREPARATION FOR THE JOINT INSPECTION

5.5.1 The joint inspection should be prepared following the “EAC SOP for Preparation of GMP Inspection” with the following particulars;

5.5.1.1 The Manufacturer or its representatives (e.g. Marketing Authorization/product registration Applicant) provides a name and contact address and available information on the manufacturing site to be inspected in a prescribed format (EAC/TF-MED/GMP/FD/FOM/N7R0).The information which have to be provided are mentioned in the relevant standard operating procedure.

5.5.1.2 The lead inspector should be the contact person for each particular joint inspection.

5.5.1.3 Each NMRAs will be in charge of the logistics arrangements of its inspectors.

5.5.1.4 At least one meeting (VC, Skype, Google hangout, etc) should be organized by the lead inspector for discussing the preparation Works of the joint inspection, which includes verification of the scope, the inspection plan, composition of the team and allocation of responsibilities.

5.6 CONDUCTING THE JOINT INSPECTION

5.6.1 The joint inspection should be conducted following the “EAC SOP for Conducting GMP Inspection” with the following particulars;

5.6.2 Inspection findings should be jointly agreed on site as is with the EAC requirements. Where applicable, according to the procedures of the EAC NMRAs, the inspection team shall provide the representative of inspected facility a written list of deficiencies at the conclusion of the inspection in a prescribed format. If agreement is not reached at this step see 5.7.

5.7 PREPARATION AND VALIDATION OF THE FINAL REPORT

5.7.1 The joint inspection report should be prepared following the “EAC SOP for Preparing and Reviewing GMP Inspection Report” with the following particulars;

5.7.2 The participating NMRAs should agree in advance establish a common list of deficiencies and to write a joint report. If any deficiency is notified according to the specific National



- requirements, this should be captured as annex of the Joint GMP Inspection Report
- 5.7.3 Taking to account, any applicable national/regional procedures, the NMRAs should consider developing a common inspection report and may find avenues to identify specific failures to specific national requirements. The Joint inspection report should be sent following the national procedures asking for Corrective and Preventive Action (CAPA) report.
- 5.7.3 On receipt of responses of findings/ observations, the participating authorities should discuss and agree the responses and any action plan proposed by the representative of inspected facility taking into account applicable national/regional procedures. If agreement is not reached among the participating authority at this step see 5.7.2
- 5.7.4 Unless otherwise agreed, separate final inspection reports (in English) in accordance with EAC requirements will be prepared to close out the inspection process, by each of the parties involved in the inspection team.
- 5.8 FOLLOW-UP OF JOINT INSPECTION**
- 5.8.1 Each participating authority is responsible for any follow-up actions according to their own regulations and procedures.
- 5.8.2 In the case of a negative inspection result, the Inspection team will liaise with each other to ensure a common understanding following “SOP for Follow up on non-compliances” and if possible an agreed conclusion before closing out the inspection and review process.
- 5.8.3 In the unlikely event of a major disagreement on the conclusion of the inspection, the authorities should proceed separately and conclude the inspection in accordance with their own national procedures.
- 5.8.4 Any joint follow-up inspection should be organized as outlined in this procedure.
- 5.9 DISSEMINATION OF THE FINAL REPORT**
- The final report should be forwarded to the NMRAs within the EAC.
- 6. REFERENCES**
- 6.1 EAC SOP for planning for an inspection
- 6.2 EAC SOP for preparing for an inspection
- 6.3 EAC SOP for conducting an inspection
- 6.4 EAC SOP for preparing and reviewing GMP inspection reports
- 6.5 EAC SOP for follow up on non-compliances.



7. REVISION HISTORY

SOP VERSION	DATE AUTHORISED	REASON FOR CHANGE	AUTHORISED BY



ANNEX 14: XIOXXIOXIXOXIXOIXO

1. BACKGROUND

- 1.1 The overall objective of EAC NMRAs joint GMP Inspections is to enhance regional collaboration so as to better distribute inspection capacity within the EAC Partner States, allowing more sites to be inspected/monitored and to reduce unnecessary duplication.
- 1.2 The expected advantages from such interactions are:
- 1.2.1 Increased dialogue between the NDRAs in EAC and the applicants from the beginning of the evaluation of a new product,
- 1.2.2 A deeper understanding of the approaches to GMP inspections by either agency,
- 1.2.3 Extending mutual confidence, and the opportunity to optimize resources and avoid unnecessary duplication of inspections.

2.0 PRINCIPLES

- 2.1 Concerned EAC authorities shall be responsible for ensuring that appropriate confidentiality arrangements are in place to allow them to conduct joint EAC NMRAs GMP inspections.
- 2.2 All participating companies shall be expected to permit unrestricted and comprehensive exchange of information between authorities.
- 2.3 The normal rules for national coordination of inspections will apply

- 2.4 The national rules for inspection fees, apply for authorities participating in any joint inspection.
- 2.5 Following a close-out of the inspection, each involved authority is responsible for administrative or enforcement actions at national level e.g. database entry, issuance/update of certificates/licenses reports.
- 2.6 Each authority reserves the right to perform its “own” inspection. However, the regulatory authorities will communicate on any deficiencies (or a negative inspection result) found. This will ensure a common understanding of the underlying facts and may assist in efforts to try to achieve a joint conclusion.
- 2.7 All the EAC Partner States NMRAs remain committed to meeting domestic process and review goals and timeframes. The joint inspection shall not adversely affect either NMRA’s ability to meet its formal domestic performance expectations.
- 2.8 All NMRAs commit to be cognizant of the other’s formal domestic performance expectations and to exhibit as much flexibility as possible in scheduling meetings and accommodating the different timeframes for the inspection.
- 2.9 All NMRAs within the EAC will make these “General Principles” public on their websites in order to make the joint GMP inspections programme, procedures and goals more transparent and to



- help answer many questions about the joint inspections programme that may exist in the general public.
- 2.10 Exchange of information on FPP/ APIs, manufacturing sites, inspection reports and other detailed information shall be subject to specific confidentiality agreements with concerned authorities and companies concerned, as necessary. All the NMRAs in the EAC will maintain the confidentiality of all such information.
- 2.11 A request for a joint inspection is no guarantee that a joint inspection will be performed. For a variety of reasons, including scheduling conflicts and available resources at any specific time, any of the NMRAs contacted for joint inspections may decline to participate. In which case, the remaining NMRAs contacted may proceed with the joint inspection.
- 2.12 If an applicant's request for a joint inspection within the EAC is declined, this will in no way affect the processing of any submission which will proceed with each agency individually, following each agency's normal procedures.
- 2.12.1 Each authority will follow the SOP for GMP inspections in the EAC.
- 2.12.2 The agencies will assure that records are maintained to facilitate the monitoring and evaluation of the program and for the assessment of the benefits and detriments of the program.



1. PARTICULARS OF APPLICANT/LICENSE HOLDER

Name _____

Physical Address _____

Country _____ Telephone _____

Fax _____ E-mail _____

2. PARTICULARS OF SITE TO BE INSPECTED

Name of site _____

Physical Address (if different from 1. above)

Country _____ Tel _____

Fax _____ E-mail: _____

Note: Separate application to be filled in for each individual site

3. APPLICATION IN EAC PARTNER STATES

Name of Country	Date of Submission



4. CONTACT PERSON ON SITE

Name of contact person _____

Tel: _____ Fax: _____

E-mail: _____

5. AUTHORISED REPRESENTATIVE/AGENT IN THE COUNTRY

Name of Local Technical Representative _____

Tel: _____

6. TYPE OF MEDICINES

Type of medicines manufactured (Tick where applicable)

(a) Human (b) Veterinary (c) Both (a) and (b)

7. REGISTRATION OF PRODUCTS

Have you registered any products in the country YES NO

Have you submitted dossier for registration? YES NO

If YES, list the products applicable. (Attach a separate sheet if needed)

.....

8. LINES TO BE INSPECTED

DOSAGE FORM	Tick where applicable	*CATEGORY	**ACTIVITIES
Tablets			
Capsules			
Injections (SVP)			
Injections (LVP)			
Oral liquids			
Creams/Ointments/Lotions			
Others (specify)			



*Category means any of the following:

Beta lactam, Non-beta lactam, Biologicals, Vaccines, Hormones, Cytotoxic products.

**Activity means any of the following:

- Formulation (dispensing, mixing, blending)
- Processing (compression, emulsification etc)
- Packing
- Quality Control
- Warehousing (raw material, finished products)

Commitment from manufacturers to welcome inspectors for inspection any time

I hereby certify that the above information is correct and apply for Good Manufacturing Practice inspection of the above-named site(s).

Signature of applicant..... Date.....

Print Name.....

Notes:

1. Please submit a copy of the Site Master File (not more than 25 pages) together with this application (refer to Guideline on preparation of a Site Master File)
2. This application must be submitted together with the appropriate fee to the Head of NMRAs

9. FOR OFFICIAL USE ONLY:

9.1 INSPECTION TYPE *(Please tick where applicable)*

- First Inspection
- Routine Re - inspection
- Joint Inspection
- Other (please specify).....
- Re - inspection after failure
- Previous inspection date.....

OFFICER ASSIGNED FOR INSPECTION

Name of the Officers:

Name	NMRA	Contact (emails & Tel)



ANNEX 15: MODEL PROCEDURE FOR COLLECTING AND HANDLING SAMPLES

1. PURPOSE

To outline the procedure that shall be followed when collecting and handling samples from the manufacturing facilities.

2. SCOPE

GMP inspection of pharmaceutical manufacturing facilities.

3. RESPONSIBILITY

GMP Inspectors

4. ACCOUNTABILITY

Head of inspection Department

5. DISTRIBUTION LIST

5.1 EAC Secretariat

5.2 GMP TWG members

5.3 GMP Inspectors

5.4 NMRA Quality Assurance

6. PROCEDURE

6.1 Inspector shall first screen the product by looking, touching packing and its contents when examining a possible suspect of substandard/spurious/falsified/fasley-labelled/counterfeit (SSFFC medicinal product.

6.2 The inspector shall look for anything, in particular its labeling and packing, that makes the product look different from an original reference sample.

6.3 Inspectors shall take sample whenever is necessary.

6.4 Special precautions to be noted by the person initiating the sampling or seizure procedure, with particular reference to correct legal procedures to be followed.

6.5 Inspectors shall inform the manufacturer reasons for taking samples

6.6 Inspectors shall make sure that all operations related to sampling are performed with care. The Inspectors should have all the tools needed for sampling according to respective product.

6.5 The actual number of tablets or capsules per sample should be decided on the basis of the type of laboratory testing to be performed and by considering the below sampling plan

**TABLE 1.SAMPLING PLAN**

DOSAGE FORM	Minimum Sample Size to Be Taken from Each Batch for Testing
Tablets/capsules	100 tablets/capsules
Suppositories/ovules	20 suppositories/ovules
Powders/sachets	20 packets/sachets
Injectables (ampules)	20 ampoules
Injectables (vials)	20 vials
Eyedrops	6 bottles
Syrups	6 bottles
IV fluids	6 bottles

- 6.6 Assign and mark each sample collected with a number from the respective Sample Receipt Form. The following sample numbering system is recommended - date, month, year, country, region, name of manufacturing facility
- 6.7 Inspector should use appropriate type of materials for sealing samples or for embargoing of products
- 6.8 The samples should be in their original packaging material. As a general rule, the packaging material should be sealed and tamperproof. The sample must be properly labeled.
- 6.9 Samples must be kept and stored according to the manufacturer's recommended storage conditions as prescribed on the product label.
- 6.10 The Inspector should make every effort to collect samples that have an "identifiable" name of the product, lot or batch number and the manufacturer's address bearing on the label.
- 6.11 Samples should be collected in their original package. In case a product which is not on its original package will need to be sampled, then Inspector should make sure that all information required should be recorded on the Sampling Form
- 6.12 Inspector should complete a Sample Receipt Form EAC/TF-MED/GMP/FD/FOM/N8R0 for each sample collected.
- 6.13 Adequate measures have to be taken to ensure that samples are transported in good condition from collection site to the respective laboratory for testing. These measures should prevent any physical damage to the samples and should comply with the manufacturer's recommended storage conditions



7.0 ATTACHMENTS

7.1 Sample Receipt Form (SRF)- EAC/TF-MED/GMP/FD/FOM/N8R0

1. Name of Institution/Company (under inspection)
- Physical Address:.....
2. Date of inspection/collecting sampled DD/MM/YYYY.....
3. Reason for collection Routine/investigational/others.....
4. Product name and description/Identification (e.g. colour, dosage form. Etc)
.....
5. Size of Batch/Lot from which sampled
6. Name and address of Manufacturer.
7. Batch no.....Manufacturing Date.....Expiring Date.....
8. Place sampled (Warehouse area, Manufacturing plant, etc.)
9. No. of samples taken (tins, packets, etc.).....
10. Sample code number.....
11. Storage conditions and precautions

Name of Representative(s) of the Inspected Establishment	Signature	Date
(1).....

Name of Drug Inspector(s) (Sampling Officer).	Signature	Date
(1).....
(2).....
(3).....



ANNEX 16: MODEL PROCEDURE FOR PREPARING AND REVIEWING GMP INSPECTION REPORTS

1. PURPOSE

The purpose of this procedure is to guide GMP inspectors and Peer review committees on how to prepare and review an inspection report respectively.

2. SCOPE

The scope of this SOP applies to the preparation and review of the GMP inspections reports of manufacturers of FPPs and of APIs applied within the EAC Partner States, including joint GMP inspection.

3. RESPONSIBILITY

- 3.13 Head of NMRAs
- 3.14 Head GMP department
- 3.15 LeadInspectors
- 3.16 GMPinspectors
- 3.17 Peer review committees

4. DISTRIBUTION LIST

- 4.1 Head of NMRAs
- 4.2 Head of GMP departments
- 4.3 NMROs
- 4.4 Joint GMP Inspection Coordinators
 - a. Quality assurance departments
- 4.5 Peer review committees

5. PROCEDURES

5.1 PREPARING A GMP INSPECTION REPORT

- 5.1.1 The GMP inspection report shall be in Times Roman 12; line spacing 1.5 and in the format attached herewith. It shall comprise the sections indicated in form EAC/TF-MED/GMP/FD/FOM/N9R0. The inspection reports should be written in 3rd person passive style and I past tense.
- 5.1.2 GMP audit reports should be written before a team proceeds to inspect the next manufacturing facility.
- 5.1.3 The inspection team shall collectively prepare and agree upon the final GMP inspection report. Any differences of opinion should be resolved by discussion.
- 5.1.4 The Lead Inspector assisted by the other inspector (s), must prepare an exit inspection report using the relevant template EAC/TF-MED/GMP/FD/FOM/N10R0. The inspectors and the inspected company should agree upon the findings and sign the exit inspection report. Any differences of opinion should be resolved by discussion and reevaluation of the finding in question. In case of any objection to sign the exit inspection report, the lead inspector should note this on the report
- 5.1.5 To prepare a GMP report, consider the documented information in the site master file, product dossier, inspection checklist, notebook,



inspection exit report, and any other document as may be necessary

review technical team within seven (7) days before discussion of report.

5.1.6 The GMP inspection report should be balanced, unbiased and factual. It shall be detailed enough to enable GMP peer review technical team make an informed opinion of the recommendation made by the inspectors. The observations should be referenced to the relevant applicable clause in the EAC GMP guideline. An observation that can't be reasonably referenced should not be listed as an observation.

5.2 REVIEWS AND APPROVAL OF THE GMP INSPECTION REPORT

5.2.1 The GMP peer review technical team, procedurally selected, shall read the reports, assess their text, context and facts and agree or disagree with the recommendations of the GMP audit team. The head of inspection to convene a meeting to discuss and approve the inspection report.

5.1.7 Where more than one observation relate to the same basic quality system failure, they should be grouped and listed as a single observation, under a heading that reflects the basic system failure.

5.2.2 The signed report must then be scanned and emailed by the Head of the NMRA to the applicant and/ or contact person in the manufacturing facility within forty five (45) days from the last day of the inspection. As necessary, the local technical representative may have a copy of the report.

5.1.8 The observations identified shall be classified according to standard procedure number EAC/TF-MED/GMP/FD/SOP/N7R0.

5.2.3 In case the facility complies with current EAC GMP requirements, the respective NMRAs will issue Certificate of Compliance as per form EAC/TF-MED/GMP/FD/FOM/N12R0.

5.1.9 The inspection team should prepare finalize, sign and submit the final GMP Inspection report within fourteen (14) working days after the date of return to office.

6.0 RECORD KEEPING

5.1.10 All inspection team members should sign the inspection report.

6.1 The GMP department/Unit/Division shall keep both an electronic copy and hard copy of the reports in PDF or any other protected format in a designated folder and prepare the certificates or cover letters of non-compliance or approval as per the GMP Inspection

5.1.11 The Lead Inspector shall submit the inspection reports to the Head GMP Inspectorate /division

5.1.12 The Head of GMP Inspectorate shall circulate copies of the report to every member of the GMP peer



6.2 The GMP inspection outcomes shall be shared with the drug registration, drug quality control and drug information department and other NMRAs in the EAC.

7.0 REFERENCE

WHO ; preparing and reviewing a GMP Inspection report

8.0 REVISION HISTORY

SOP VERSION	DATE AUTHORISED	REASON FOR CHANGE	AUTHORISED BY

9.0 ATTACHMENTS

- 9.1 Template for FPP/API Inspection Report: EAC/TF-MED/GMP/FD/N6RO
- 9.2 EAC GMP Inspection Exit Points: EAC/TF-MED/GMP/FD/FOM/N10RO
- 9.3 Covering letter for Inspection Reports Compliance: EAC/TF-MED/GMP/FD/FOM/N11R0
- 9.4 Certificate of Compliance to GMP: EAC/TF-MED/FD/FOM/N12R0



COVER PAGE

The page should bear the name of the Regulatory Authority

Name and details of the company/facility inspected

Details of the audited manufacturing site;

Name of the site, geographical location (district, state and country),
inspection dates; (Date/s, Month and Year)

1.0 INTRODUCTION

1.1 General information

Name of Manufacturer:

Physical address:

Unit number:

Production Block:

Contact person and email address (full Postal address, Tel numbers, faxes and email address)

Manufacturing license:

GMP certificate:

1.2 Inspection date(s) Date(s), Month.....Year.....

1.3 Type of inspection:

1.4 Abbreviations used

All the abbreviations used in the report should be included in this section.

1.5 Inspection Teams-

Name of the GMP Inspectors involved. The team leader should be specified.

1.6 Names, titles and qualifications of key personnel of the facility that participated

Other people met during the inspection should also be mentioned. Key personnel



PART 2: SUMMARY

2.1 General information about the company and site

Short description of the company and the activities undertaken.

Dosage forms(s) included in the inspection

1.5 Summary of the activities performed by the manufacturer (Manufacturing, packaging etc)

2.2 History of regulatory agency inspections

Where applicable, the date of previous inspection by the regulatory authority

Conclusion of other inspections

Where applicable, State major changes made on the facility, equipment, products, and senior personnel since the previous inspection should be stated.

2.3 Scope of the inspection

Brief description of the objective/reason for the Inspection. State the type of inspection and whether it was product related inspection.

What you planned to do, areas inspected.

3.1 INSPECTION - OBSERVATIONS AND FINDINGS

Specify each area of the facility that was inspected. Use headings from the checklist relevant to the scope of the inspection. New headings may be introduced where necessary. The following area should however be covered adequately.

Add Appendixes if relevant

Refer to applicable clause in GMP Guideline

QUALITY ASSURANCE

GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

SANITATION AND HYGIENE

QUALIFICATION AND VALIDATION

COMPLAINTS

PRODUCT RECALLS



CONTRACT PRODUCTION AND ANALYSIS

SELF INSPECTION AND QUALITY AUDIT

PERSONNEL

TRAINING

PERSONAL HYGIENE

PREMISES

EQUIPMENT

MATERIALS

DOCUMENTATION

GOOD PRACTICES IN PRODUCTION

GOOD PRACTICES IN QUALITY CONTROL

3.2 SUMMARY OF SIGNIFICANT DEFICIENCIES

Where observation of non-compliance to GMP are made they shall be listed in order of importance and classified as critical, major, minor as in Appendix E

4.0 RECOMMENDATIONS AND CONCLUSION

Recommendations

State any recommendations or actions to be taken by against the facility.

Conclusion

Make conclusion of your assessment of the acceptability of the facility's GMP status for the range of products manufactured.

Consider the examples below from EAC PPQ

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the inspection report, were considered to be operating at an acceptable level of compliance with EAC GMP guidelines.



However, the observations (non-compliances with guidelines) listed below must be addressed in a timely manner. The manufacturer is expected to respond to all observations and for each include a description of the corrective action implemented or planned to be implemented, and the date of completion or target date for completion. The acceptability of corrective actions will be assessed through evaluation of the response to each observation and will be followed up during the next inspection.

or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, a decision on the compliance of with WHO GMP will be made after the manufacturer's response to the observations has been assessed.

The manufacturer is expected to respond to all observations and for each include a description of the corrective action implemented or planned to be implemented, and the date of completion or target date for completion. In addition, for observations classified as "major", supporting documentation should be submitted with the response as objective evidence of completion of corrective actions. The acceptability of corrective actions will be assessed through evaluation of the response to each observation and will be followed up during the next inspection. If considered necessary, an on-site follow up inspection may be conducted to verify effective implementation of corrective actions.

or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection report, was considered to be operating at an unacceptable level of compliance with EACGMP guidelines.

Another inspection will be required to verify the implementation of corrective actions before the manufacturer's level of GMP compliance can be reconsidered.

5.0 APPENDIXES

Attach the necessary Appendixes to the report, chronologically numbered in Roman numerals. The following Appendixes should appear:

Manufacturing certificate
GMP certificate of the local regulatory authority

6.0 NAMES, DESIGNATION, SIGNATURES AND DATE

The report should be signed and dated by the GMP Inspectors involved.



Date:

Name and Address of the facility:			
Item(s) requiring attention:		Action(s) agreed to be taken:	
Name of inspector:	Signature:	Name of inspectee:	Signature:
1.....	1.....
2.....	2.....
3.....	3.....

Date.....
Continuation sheet.....

Item(s) requiring attention:		Action(s) agreed to be taken:	
Name of inspector:	Signature:	Name of inspectee:	Signature:
1.....	1.....
2.....	2.....
3.....	3.....



Your Ref:.....

Date.....

ADDRESS OF THE FACILITY

.....
.....

Attn: PLANT COORDINATOR

REPORT OF cGMP INSPECTION REPORT

The manufacturing facility of
..... (physical address), of
..... (Country), inspected on
..... (dates), complied with cGMP requirements as per
NMRA GMP Guidelines at the time of inspection for the following dosage
(category) production lines:

Mention the lines

.....
.....
.....

Attached please find the inspection report. Attention should be given to the noted deficiencies and corrective action taken on the major and minor deficiencies observed in due course. Please send the corrective action schedule and documentation of what has been done.

Please note:

1. That each product must be registered with NMRA (mention the name) before export to (Country name)
2. NMRA (mention name) can inspect your facility at any time as long as your product is on the..... (country name) market.
3. Approval for GMP compliance is valid for three years from the date of inspection.

The company has to apply for re-inspection six months prior to the expiry date if interested in maintaining products on the NMRA (mention name of NMRA) register.

.....
Head of NMRA (name & Signature)

Copy: Local Agent

**CERTIFICATE OF GOOD MANUFACTURING PRACTICES****(Issued under NMRA regulations)**

On the basis of the inspection carried out on [date] we certify that the site indicated on this certificate complies with Good Manufacturing Practices for dosage forms, categories and activities listed in Table 1.

1. Name and physical address of site :
2. Manufacturer's license number :

Table 1:

Dosage form (s)	Categories of medicines	Activity i.e. Packaging, manufacture of finished pharmaceutical products

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured lies with the manufacturer/applicant.

This certificate remains valid until [date] It becomes invalid if the dosage forms, activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Name of Head of NMRA

.....
Signature

.....
Stamp and date:

- Note:**
1. This certificate certifies the status of the site listed in point 1 of the certificate
 2. This certificate shall remain valid for a period of 3 years from the date of issue, but can be revoked at any time if there is evidence that the facility is no longer complies with then current EAC GMP regulations.

Example of Table 1:

Dosage form (s)	Category (ies)	Activity (ies)
Tablets	Cytotoxic	Packaging
	Hormone	Production, packaging and quality control
	Penicillin	Re-packaging and labeling
Injectables	Cephalosporin	Aseptic preparation, filling, packaging, labelling



ANNEX 17: MODEL PROCEDURE FOR RISK CLASSIFICATION OF GMP DEFECIENCIES

1. PURPOSE

The purpose of this guide is to ensure uniformity among the EAC GMP inspectors in classifying observations and in determining the compliance status of pharmaceutical industries following GMP inspection.

2. DEFINITIONS

2.1 Critical observation:

An observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

2.2 Major observation:

An observation describing a situation that may have an impact on the product but is not as significant as a critical observation. It may have an indirect impact in the strength, identity, purity or safety of the product. There is reduced usability of the product without a probability of causing harm to the consumer. Observation of a major deficiency puts a question mark on the reliability of the firm's quality assurance system.

2.3 Minor observation:

An observation describing a situation that is a departure from GMP but has no significant impact on the product quality. It has low probability of affecting the quality or usability of the product.

2.4 Critical product:

A critical product is one for which one or more of the following criteria apply:

- 2.4.1 Narrow therapeutic window
- 2.4.2 High toxicity
- 2.4.3 Sterile product
- 2.4.4 Biological product
- 2.4.5 Complex manufacturing process: process for which slight deviations in the control of parameters could result in a non-uniform product or a product not meeting its specifications. As examples, powder mixing or granulation for low dosage solid forms, long acting/ delayed action products, sterile products.

2.5 Non-compliant product:

is a product that does not meet the manufacturer's specifications or those in the authorized pharmacopeia

3. GUIDE

Whereas it is recognized that it is impossible to encompass every situation that may generate a risk, the following principles should be considered:

- 3.1 Classification of the observation is based on the assessed risk level and the number of occurrences. This may vary depending on the nature of the product, eg in some circumstances an example of major deficiency may be categorized as critical.
- 3.2 A deficiency that was reported at a previous inspection and



not corrected may be reported in a higher classification of observation.

3.3 Generally, a GMP non-compliance (NC) rating is assigned when a critical observation is noted during an inspection.

3.4 Generally, a GMP compliance (C) rating is assigned when major observations are noted during an inspection after submission and satisfactory review of Corrective Action and Preventive Action. However, a NC rating may be assigned in the following situations;

3.4.1 When numerous major observations are noted during an inspection indicating that the company does not control its process and operations sufficiently.

3.4.2 Repetition of major observations noted during previous inspections indicating that the company did not:

a) Implement the corrective actions submitted following the previous inspections.

b) Did not put in place adequate preventive actions in a timely manner to avoid recurrence of such deviations.

3.4.3 A compliance rating of GMP compliance will be assigned in all situations where only minor observations are noted.

3.5 Critical Observations

3.5.1 Premises:

3.5.1.1 No air filtration system to eliminate airborne contaminants that are likely to be generated during manufacture or packaging.

3.5.1.2 Generalized malfunctioning of the ventilation system(s) with evidence of widespread cross-contamination.

3.5.1.3 Design of premises does not allow unidirectional flow of material and personnel thus posing a risk of cross contamination

3.5.1.4 The building material for premises not fit for pharmaceutical industry e.g asbestos roofing

3.5.1.5 Inadequate segregation of manufacturing and of testing areas from other manufacturing areas for products that pose serious health hazards such as:

a) Highly sensitizing drugs

b) Biologicals

c) Hormones

d) Cytotoxic drugs

e) Highly active drugs

3.5.2 Equipment:

3.5.2.1 Equipment used for manufacturing operations of critical products not qualified with evidence of malfunctioning.



- 3.5.2.2 Evidence of contamination of products by foreign materials such as grease, oil, rust particles from the equipment.
- 3.5.2.3 Equipment made of inappropriate material.
- 3.5.3 Personnel**
- 3.5.3.1 Individual in charge of Quality Control/ Quality Assurance or production does not hold a university degree in a science related to the work being conducted and does not have sufficient practical experience in their area of responsibility.
- 3.5.4 Sanitation**
- 3.5.4.1 Evidence of widespread accumulation of residues/ extraneous matter indicative of inadequate cleaning.
- 3.5.4.2 Evidence of gross infestation.
- 3.5.5 Raw material testing**
- 3.5.5.1 Evidence of falsification or misrepresentation of analytical results.
- 3.5.5.2 No evidence of certificate of analysis (CoA) available from the supplier/synthesizer and no testing done by the manufacturer.
- 3.5.6 Manufacturing control**
- 3.5.6.1 No written Master Formula.
- 3.5.6.2 Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.
- 3.5.6.3 Line clearance not properly done leading to cross contamination
- 3.5.6.4 Inappropriate status labelling and identification of materials in production leading to mix ups
- 3.5.6.5 Lack of proper controls in handling starting materials, in process bulk materials and materials in quarantine or rejected areas
- 3.5.7 Quality Control Department**
- 3.5.7.1 No full-time person in charge of QC.
- 3.5.7.2 QC department not a distinct and independent unit, lacking decisional power, with evidence that QC decisions are overruled by production department or management.
- 3.5.7.3 Poor quality control methods such as analytical methods used in the analysis of starting and finished products are not appropriate, analytical methods not validated, major equipment for analysis has no installation and/or operation qualification
- 3.5.8 Finished Product Testing**
- 3.5.8.1 Finished product not tested for compliance with specifications by the manufacturer before release for sale.
- 3.5.8.2 Evidence of falsification or misrepresentation of testing results/ forgery of CoA.

**3.5.9 Records**

- 3.5.9.1 Evidence of falsification or misrepresentation of records.

3.5.10 Stability

- 3.5.10.1 No data available to establish the shelf-life of products.
- 3.5.10.2 Evidence of falsification or misrepresentation of stability data/ forgery of CoA.

3.5.11 Sterile Products

- 3.5.11.1 Critical sterilization cycle based on probability of survival not validated.
- 3.5.11.2 Water for injection (WFI) systems not validated with evidence of problems such as microbial/ endotoxin counts not within specifications.
- 3.5.11.3 No media fills performed to demonstrate the validity of aseptic filling operations.
- 3.5.11.4 No environmental controls/no monitoring of viable microorganisms during filling for aseptically filled products.
- 3.5.11.5 Aseptic filling operations maintained following unsatisfactory results obtained for media fills.
- 3.5.11.6 Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.
- 3.5.11.7 Inadequate room classification for processing /filling operations.

- 3.5.11.8 Aseptic manufacturing suites under negative pressure compared to clean (C-D) areas. Clean (C-D) areas under negative pressure to unclassified areas.

3.6 Major Observations**3.6.1 Premises**

- 3.6.1.1 Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.
- 3.6.1.2 Maintenance/periodic verification such as air filter replacement, monitoring of pressure differentials not performed.
- 3.6.1.3 Accessory supplies (steam, air, nitrogen, dust collection etc) not qualified.
- 3.6.1.4 Heating Ventilation Air Conditioning (HVAC) and purified water (PW) system not qualified.
- 3.6.1.5 Temperature and humidity not controlled or monitored when necessary.
- 3.6.1.6 Damages to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed.
- 3.6.1.7 Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.
- 3.6.1.8 Surface finish (floors, walls, ceilings) that do not permit effective cleaning.*



- 3.6.1.9 Unsealed porous finish in manufacturing areas with evidence of contamination (mould, powder from previous productions etc).*
- 3.6.1.10 Insufficient manufacturing space that could lead to mix ups.*
- 3.6.1.11 Quarantine areas accessible to unauthorized personnel and not well marked.*
- 3.6.1.12 No separate area/Insufficient precautions to prevent contamination or cross-contamination during RM sampling.

3.6.2 Equipment

- 3.6.2.1 Equipment does not operate within its specifications.*
- 3.6.2.2 Equipment used for complex manufacturing operation not qualified.
- 3.6.2.3 Clean in place (CIP) equipment not validated.
- 3.6.2.4 Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.
- 3.6.2.5 Stored equipment not protected from contaminations.*
- 3.6.2.6 Inappropriate equipment for production: surfaces porous and non-cleanable/material to shed particles.*
- 3.6.2.7 No covers for tanks, hoppers or similar manufacturing equipment.

- 3.6.2.8 Equipment location does not prevent cross-contamination or possible mix ups for operations performed in common area.
- 3.6.2.9 PW not maintained or operated to provide water of adequate quality.*
- 3.6.2.10 Leaking gaskets.
- 3.6.2.11 No calibration program for measuring equipment /no records maintained.*
- 3.6.2.12 No equipment usage logs.

3.6.3 Personnel

- 3.6.3.1 Delegation of responsibilities for QC or production to insufficiently qualified persons.
- 3.6.3.2 Insufficient personnel in QC production resulting in a high possibility of error.
- 3.6.3.3 Insufficient training for personnel involved in production and QC resulting in related GMP violations.
- 3.6.3.4 No medical check-ups for personnel involved in critical areas of production and quality control

3.6.4 Sanitation

- 3.6.4.1 Sanitation program not in writing but premises in acceptable state of cleanliness.
- 3.6.4.2 No Standard Operating Procedure (SOP) for microbial/environmental monitoring, no action limits for areas where susceptible non-sterile products are manufactured.



3.6.4.3 Cleaning procedure for production equipment not validated (including analytical methods).

3.6.4.4 Incomplete health requirements.

3.6.5 Raw Material Testing

3.6.5.1 Water used in the formulation is not of acceptable quality.

3.6.5.2 No testing done on materials by the manufacturer.

3.6.5.3 COA showing incomplete testing.

3.6.5.4 Incomplete specifications.

3.6.5.5 Specifications not approved by QC.

3.6.5.6 Testing methods not validated.

3.6.5.7 Use of materials after retest date without retesting.

3.6.5.8 Multiple lots comprising one consignment not considered as separate for sampling, testing and release.

3.6.5.9 No SOP for conditions of transportation and storage.

3.6.6 Manufacturing Control

3.6.6.1 Master Formulae prepared/verified by unqualified personnel.

3.6.6.2 Deviations from instructions during production not documented and not approved.

3.6.6.3 Discrepancies in yield or reconciliation following production not investigated.

3.6.6.4 Line clearance between productions of different products not covered by SOP and not documented.

3.6.6.5 No regular checks for measuring devices/no records.

3.6.6.6 Lack of proper identification of in-process materials and products resulting in a high probability of mix-ups.

3.6.6.7 Inadequate labelling /storage of rejected materials and products that could generate mix-ups.

3.6.6.8 Upon receipt, bulk and in-process drugs, raw materials and packaging materials not held in quarantine until released by QC.

3.6.6.9 Production personnel using bulk and in-process drugs, RM and packaging materials without prior authorization by QC.*

3.6.6.10 Inadequate/inaccurate labelling of bulk/in-process drugs, raw materials and packaging materials.

3.6.6.11 Raw materials dispensing not done by qualified persons, according to SOP.

3.6.6.12 Master Formulae incomplete or showing inaccuracies in the processing operations.

3.6.6.13 Changes in batch size not prepared/verified by qualified personnel

3.6.6.14 Inaccurate/incomplete information in manufacturing/packaging batch document.



- 3.6.6.15 Although documented, combination of batches done without QC approval/not covered by SOP.
- 3.6.6.16 No written procedures for packaging operations.
- 3.6.6.17 Non-standard occurrences during packaging not investigated by qualified personnel.
- 3.6.6.18 Inadequate control of coded and non-coded printed PM (including storage, dispensing, printing and disposal).
- 3.6.6.19 No or inadequate self-inspection program does not address all applicable sections of GMPs/ Records incomplete or not maintained.
- 3.6.7 Recall**
- 3.6.7.1 Absence of recall procedure combined with distribution practices that would not permit and adequate recall (distribution records unavailable or not kept).
- 3.6.7.2 Improper quarantine and disposal practices that would allow recalled/ rejected units to be returned for sale.
- 3.6.8 Quality Control/Quality Assurance Department**
- 3.6.8.1 Inadequate facilities, personnel and testing equipment.
- 3.6.8.2 No authority for QC/QA personnel to enter production areas.*
- 3.6.8.3 No SOP approved and available for sampling, inspection and testing of materials.
- 3.6.8.4 Products made available for sale without approval of QC department.*
- 3.6.8.5 Products released for sale by QC without proper verification of manufacturing and packaging documentation.
- 3.6.8.6 Deviations and borderline conformances not properly investigated and documented, according to an SOP.
- 3.6.8.7 Raw materials and packaging materials used in production without prior approval of QC.
- 3.6.8.8 Reprocessing/Reworking done without prior approval of QC.*
- 3.6.8.9 No system for complaint handling and returned goods.
- 3.6.8.10 SOPs covering operations that can affect the quality of a product such as transportation, storage etc not approved by QC / not implemented
- 3.6.8.11 Absence of a change control system.
- 3.6.8.12 The systems and controls in place for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable.

**3.6.9 Packaging Material Testing**

- 3.6.9.1 Absence of testing of packaging materials.
- 3.6.9.2 Specifications not approved by QC.

3.6.10 Finished Product Testing

- 3.6.10.1 Incomplete/inadequate specifications.
- 3.6.10.2 Finished products specifications not approved by QC.
- 3.6.10.3 Incomplete testing.
- 3.6.10.4 Test methods not validated.

3.6.11 Records

- 3.6.11.1 Absence of Master Production Documents.
- 3.6.11.2 Lack of standard operating procedures for the operations undertaken

3.6.12 Samples

- 3.6.12.1 Retention samples not kept for finished products.

3.6.13 Stability

- 3.6.13.1 Insufficient number of batches/ insufficient data to establish shelf life.
- 3.6.13.2 No action taken when data shows that the products do not meet their specifications prior to the expiry date.

- 3.6.13.3 No stability studies pertaining to changes in manufacturing (formulation) packaging materials.

- 3.6.13.4 Testing methods not validated.

3.6.14 Sterile Products

- 3.6.14.1 Aqueous based products not subjected to terminal steam sterilization without proper justification or approval through the marketing authorization.

- 3.6.14.2 Insufficient number of samples for room classification/inadequate sampling methods.*

- 3.6.14.3 Insufficient environmental controls/ insufficient monitoring of viable micro-organisms during filling for aseptically filled products.*

- 3.6.14.4 Premises and equipment not designed or maintained to minimize contamination/generation of particles.*

- 3.6.14.5 Inadequate maintenance of purified water and water for injection systems.

- 3.6.14.6 Inadequate re-validation of purified water and water for injection systems after maintenance, upgrading, out-of-specs trends.

- 3.6.14.7 Inadequate training of personnel.

- 3.6.14.8 Inadequate gowning practices for clean and aseptic areas.

- 3.6.14.9 Inadequate practices/precautions to minimize contamination or prevent mix-ups.



3.6.14.10 Non-validated time lapse between start of manufacturing and sterilization or filtration.

3.6.14.11 Inadequate procedures for media-fills.

3.6.14.12 Insufficient number of units filled during media-fills.

3.6.14.13 Media-fills do not simulate actual operations.

3.6.14.14 Capability of media to grow a wide range of microorganisms not demonstrated.

3.6.14.15 Misinterpretation of results for media-fills.

3.6.14.16 Absence of leak test for ampoules.

3.6.14.17 Samples for sterility testing insufficient in number or not representative of the entire production run.

3.6.14.18 Each sterilizer load not considered as a separate batch for sterility testing.

3.6.14.19 Purified water is not used as the feed water for water for injection system and the clean steam generator.

3.6.14.20 The water for injection used in the preparation of parenterals is not tested for endotoxins.

3.6.14.21 The water for injection used for final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and

components are not depyrogenated subsequently.

***May be elevated to critical observation**

3.7 Minor Observations

3.7.1 Premises

3.7.1.1 Doors giving direct access to exterior from manufacturing and packaging areas used by personnel.

3.7.1.2 Un-screened/un-trapped floor drains.

3.7.1.3 Outlets for liquids and gases not identified.

3.7.1.4 Damages to surfaces not directly adjacent or above exposed products.

3.7.1.5 Non-production activities performed in production areas.

3.7.1.6 Inadequate rest, change, wash-up and toilet facilities.

3.7.2 Equipment

3.7.2.1 Insufficient space between equipment and walls to permit cleaning.

3.7.2.2 Base of immovable equipment not adequately sealed at points of contact.

3.7.2.3 Use of temporary means or devices for repair.

3.7.2.4 Defective or unused equipment used for non-critical products not qualified.

**3.7.3 Sanitation**

- 3.7.3.1 Incomplete written sanitation program but premises in acceptable state of cleanliness.
- 3.7.3.2 Sanitation or Health and hygiene programs not properly implemented or followed by employees.

3.7.4 Raw Material Testing

- 3.7.4.1 Incomplete validation of test methods.

3.7.5 Manufacturing Control

- 3.7.5.1 Incomplete SOPs for handling of materials and products.
- 3.7.5.2 Access to production areas not restricted to authorized personnel.
- 3.7.5.3 Inadequate checks for incoming materials.
- 3.7.5.4 Written procedures incomplete for packaging operations.
- 3.7.5.5 Incomplete recall procedure.

3.7.6 Packaging Material Testing

- 3.7.6.1 Inadequate procedures of transportation and storage.
- 3.7.6.2 Inadequate handling of outdated/ obsolete packaging materials.
- 3.7.6.3 Incomplete testing.
- 3.7.6.4 Inadequate specifications.

3.7.7 Finished Product Testing

- 3.7.7.1 Incomplete testing of physical parameters.

3.7.8 Records

- 3.7.8.1 Incomplete records/documentation for a product.
- 3.7.8.2 Incomplete plans and specification for the manufacturing buildings.
- 3.7.8.3 Incomplete documentation pertaining to supervisory personnel.
- 3.7.8.4 Insufficient retention time for evidence and records to be maintained.
- 3.7.8.5 No organization charts.
- 3.7.8.6 Incomplete records for the sanitation program.

3.7.9 Samples

- 3.7.9.1 Samples of raw materials not available.
- 3.7.9.2 Incomplete testing parameters.
- 3.7.9.3 Improper storage conditions.

3.7.10 Stability

- 3.7.10.1 Insufficient number of batches in continuing stability program.
- 3.7.10.2 Incomplete testing parameters.
- 3.7.10.3 Improper storage conditions.



3.7.11 Sterile Products

- 3.7.11.1 Steam used for sterilization not monitored to assure suitable quality and absence of additives.
- 3.7.11.2 Inadequate control on the maximum number of personnel present in clean and aseptic areas.
- 3.7.11.3 Gases used to purge solutions or blanket products not passed through a sterilizing filter.
- 3.7.11.4 Inadequate inspection for particles and defects.





ANNEX 18: MODEL PROCEDURE FOR FOLLOW UP ON NON-COMPLIANCES AFTER GMP INSPECTION

5. PURPOSE

The purpose is to outline procedures for National Medicines Regulatory Authorities (NMRAs) to follow up on non-compliances observed after GMP inspections of manufacturing facilities and implement administrative actions where necessary.

6. SCOPE

The scope of this SOP applies to EAC GMP inspections of manufacturers of FPPs and of APIs.

7. RESPONSIBILITY

7.1 Head of NMRA

7.1.1 Ensure decisions on all manufacturing facilities are implemented in a timely manner and in accordance with the legislation to protect human health

7.2 Head GMP Inspectorate:

7.2.1 Ensuring that administrative or enforcement actions are undertaken as appropriate

7.3 The lead and/or co-inspector:

7.3.1 To generate a GMP inspection report with conclusion on the status of the manufacturing facility

7.3.2 To review the CAPA and submit comments

7.4 The Peer Review/Technical Committee:

7.4.1 To review the inspection report and make a final conclusion on the submitted GMP inspection report

7.5 GMP unit/division/section administrative staff

7.5.1 Update databases and prepare communication by letter or email

8. DISTRIBUTION LIST

4.1 Head of NMRA

4.2 Head of GMP inspectors

4.3 GMP inspectors

4.4 The peer review/technical committee members

4.5 GMP unit/division/section administrative staff

9. PROCEDURE

5.1 After generation of a GMP inspection report with classification of all non-compliances as critical, major and minor therein and peer review; a site shall be considered compliant if it has:

5.1.1 No critical noncompliance.

5.1.2 Minor non compliances

5.1.3 Major non compliances that are rectified and Corrective And Preventive Action (CAPA) submitted by the manufacturer; review of CAPA by the NMRA and found satisfactory



5.2 A site shall be considered non-compliant if it has:

- 5.2.1 One or more critical non compliances
- 5.2.2 Several major non compliances that imply a failure in the quality assurance system
- 5.3 The NMRA shall issue a GMP certificate and /or a manufacturing license where applicable for a site that is compliant i.e has no critical or has minor observations
- 5.4 The NMRA shall demand for a corrective and preventive action report for review and where possible a follow up inspection for a site that has major non compliances may be done prior to issue of a GMP certificate and close out of the inspection.
- 5.5 The NMRA shall not issue a GMP certificate to a non-compliant manufacturing facility that has critical or several major non compliances
- 5.6 Local manufacturers shall require physical re-inspection for a site that has critical or several major non compliances until a satisfactory report is achieved
- 5.7 The re-inspection of a non-compliant facility shall be after submission of corrective action report and an application together with payment of the inspection fee.

5.8 Manufacturing facilities that fail to comply with GMP shall have:

- 5.8.1 their products removed from the national medicine register thus halting further manufacture or importation of the products
- 5.8.2 Their products recalled from the market depending on the criticality of the findings (see SOP on recall of products from the market annex VI H).
- 5.9 The NMRA may decide to close down the whole site by withdrawing the GMP certificate and/or manufacturing license or a section of the site depending on the critical observations identified by the inspection team
- 5.10 Upon careful consideration of the findings in the inspection report and where these affect the health of patients in a critical manner; the NMRA may consider raising a rapid alert to EAC NMRAs, health care workers and patients

6. RECORDS

- 6.1 The quality manuals, master distribution list file, obsolete documents file and general list of documents shall be kept and maintained by HQM for a period specified in the respective document



- 6.2 Department list of documents shall be kept and maintained by respective Head Department
- 6.3 Records shall be destroyed by tearing/shredding/burning or any other appropriate means.

7. REFERENCES

- 7.1. Inspection procedures NDA-Uganda
- 7.2. EMA Compilation of Community procedures on Inspection and exchange of information, 16 July 2012, EMA/INS/GMP/321252/2012 Rev 15, Compliance and Inspection

8.0 REVISION HISTORY

SOP VERSION	DATE AUTHORISED (Name, Sign & Date)	REASON FOR CHANGE	AUTHORISED BY (Name, Sign & Date)



ANNEX 19: MODEL PROCEDURE FOR HANDLING PRODUCT RECALL

1. PURPOSE

To outline the procedure for classification and communications involved in a product recall or withdrawal

2. SCOPE

This SOP is applicable for use at EAC headquarter and individual Partner States NMRAs for handling product recalls occurring in their operations. They are also applicable to all authorized and marketed products for which there is an evidence or potential that the product is noncompliant with the marketing authorization and, therefore can have undesirable effects to the patient's health.

3. RESPONSIBILITY

It is the responsibility of the head of NMRA and the pharmaceutical Inspectorate secretariat to initiate and supervise the product recall or withdrawal.

It is also the responsibility of the manufacturer/or distributor /or Local Technical Representative to inform the NMRA of any product defect and conduct the recall of the defected products

4. ACCOUNTABILITY

- Head NMRA (HNMRA)

5. DISTRIBUTION

- Head of NMRA
- Head of Inspectorate
- Head of registration
- Head of Medicines Information

6. PROCEDURE

6.1 OCCASIONS UNDER WHICH A PRODUCT MAY BE RECALLED OR WITHDRAWN

- 6.1.1. The withdrawal/recall of a particular batch or batches of a product from the market may be occasioned by the following:
 - 6.1.1.1. Serious reports of adverse drug reactions not included in the package insert
 - 6.1.1.2. Unexpected frequency of adverse reaction stated in the package inserts
 - 6.1.1.3. Incorrect labeling of a product
 - 6.1.1.4. Incorrect formulation of a product
 - 6.1.1.5. Unfavorable result from post marketing surveillance

6.2. CLASSIFICATION OF DEFECTS

It is necessary to assign/indicate the relative degree of health hazard presented by the product being recalled, namely:

- 6.2.1. Situation in which there is reasonable probability that the use of or exposure to a suspect product will cause serious adverse health consequences or death
- 6.2.2. Situation in which the use of or exposure to a suspect product will cause temporary adverse health consequences or where the probability of serious adverse health consequences is remote.



- 6.2.3. Situation in which the use of or exposure to a suspect product is not likely to cause any adverse health consequences

The following classification criterion is recommended:

Class I

Class I is for defective/dangerous/potentially life threatening medicines that predictably or probably could result into serious health risk/ adverse events or even death.

Class II

Class II is for medicines that possibly could cause temporary or medically reversible adverse health problem or mistreatment.

Class III

Class III is for medicine that is defective and is unlikely to cause any adverse health reaction or which do not comply with the requirements of the NMRA Laws of the individual partner States and regional bidding laws and regulations of the EAC

6.3. TYPES OF RECALL

6.3.1. Type A

A type A recall is designed to reach all suppliers of medicines (all distribution points) i.e. wholesalers throughout the country, directors of hospital services (private as well as state hospitals), retail outlets, doctors, nurses, pharmacists, authorized prescribers and dispensers and individual customers or patients through media release (radio, television, internet, regional and national press).

Action: Recall Notification to all distribution points plus Media release.

6.3.2. Type B

A type B recall is designed to reach wholesalers throughout the country, directors of hospital services (private as well as state hospitals), retail outlets, doctors, nurses, pharmacists, authorized prescribers and dispensers.

Action: Recall letter to all distribution points.

6.3.3. Type C

A type C recall is designed to reach wholesale level and other distribution points (e.g. pharmacies, doctors, hospitals). This can be achieved by means of representatives calling on wholesalers and/or retail outlets. If it is known where the product in question had been distributed to, specific telephone calls or recalls letters to arrange for the return of the product could be made.

Action: Specific telephone calls, recall letters/ representatives calling at distribution points if known where the medicines have been distributed.

6.4. RECALL NOTIFICATION

It is imperative that before or upon initiating a recall, the company immediately on becoming aware of the problem, notifies the head NMRA or, in his absence, his designate

If the notification fails and there is urgent need to recall the product then the company may proceed according to their discretion and follow up contact with the NMRA to be pursued in the process.



6.5. BASIC INFORMATION REQUIRED FOR RECALL

- 6.5.1. Name, strength, pack size, batch/ lot number and means of identification of the recalled product
- 6.5.2. Total quantity of the product being re called originally in possession of the company
- 6.5.3. The date distribution of the product began
- 6.5.4. The total quantity of the product being re called that had been distributed up to the time of the recall should be indicated.
- 6.5.5. Area of distribution of the product and, if exported, the country to where it was exported.
- 6.5.6. List of customers to whom product was issued
- 6.5.7. The quantity of the recalled product still in their possession
- 6.5.8. The reason for initiating the recall; nature of defect
- 6.5.9. Suggested action to be taken and its urgency
- 6.5.10. Indication of the health risk together with reasons

6.6. HEALTH HAZARD EVALUATION

Before initiating a recall, the company will gather, correlate and evaluate all known information on the nature and extent of the reputed health risk. An evaluation of the health hazard presented by a product being recalled

or considered for recall will also be conducted by the NMRA and will take into account, but need not be limited to, assessment of the following factors:

- 6.6.1. Whether any disease or injuries have already occurred from the use of the product
- 6.6.2. Hazard to various segments of the population e.g. children, surgical patients etc, who are expected to be exposed to the product, with particular attention to those individuals who may be at greatest risk
- 6.6.3. The degree of seriousness of the health hazard to which the population at greatest risk would be exposed.
- 6.6.4. The likelihood of occurrence of that hazard
- 6.6.5. The consequences (immediate or long-term) of occurrence of the hazard. The recalling company will be given every opportunity to contribute to the information on which the health hazard evaluation is made by the NMRA, who, on the basis of this determination, classifies it based on the relative degree of health hazard posed by the product being recalled or considered for recall.

6.7. RECALL STRATEGY

In formulating a recall strategy, the following should be taken into consideration:



- 6.7.1. Result of health hazard evaluation
- 6.7.2. Ease in identifying the product
- 6.7.3. Extent to which the product deficiency is obvious to the consumer/user
- 6.7.4. Continued availability of essential products (risk: benefit)

6.8. ELEMENTS OF A RECALL STRATEGY

6.8.1. Depth of recall

Depending on the product's degree of hazard and extent of distribution, the recall strategy has to specify the level in the distribution chain in which the recall is to extend, as follows:

- 6.8.2. Consumer or user level including any intermediate wholesale and/ or distribution or retail level, and or all government and military hospitals; or
- 6.8.3. Retail level, including any intermediate wholesale and/ or distribution level; or
- 6.8.4. Manufacturer, Wholesale and/ or distributor level.
- 6.8.5. **Recall communication** from recalling company to all affected parties

6.9. RECALL COMMUNICATION

A recalling entity is responsible for promptly notifying involved parties about the recall and the same information notified to the Board. The format, content, and extent of recall communication should be commensurate

with the hazard of the product and the strategy developed for that recall. Recall communication should convey:

- 6.9.1. That the product in question is subject to recall
- 6.9.2. That further distribution or use of any remaining product should cease immediately
- 6.9.3. The instructions on what to do with the product

6.10. IMPLEMENTATION OF RECALL COMMUNICATION

The following may be used in a recall communication:

- 6.10.1. Telephone
- 6.10.2. Telex
- 6.10.3. Telegram
- 6.10.4. Public media
- 6.10.5. Special delivery
- 6.10.6. Conspicuous marking e.g. "MEDICINE RECALL" in bold red on the letter and envelope, and also "URGENT" for serious cases
- 6.10.7. A public warning may be necessary for products that pose serious health hazards. However, this should be reserved for urgent situations where other means of preventing use of the recalled product appear inadequate.



NMRA to decide if necessary and who to issue such a warning and the type of public warning should be specified in the recall strategy for the product e.g.

General public warning in the general media as appropriate and a public warning through specialized news media to professionals or to specific segments of the population like physicians, hospitals etc.

6.11. CONTENTS OF RECALL COMMUNICATION

A recall communication should:

- 6.11.1. Be brief and to the point
- 6.11.2. Name the product, strength, pack size, and any other pertinent descriptive information of the product
- 6.11.3. Indicate nature of the defect
- 6.11.4. Specify urgency of the action
- 6.11.5. Indicate reason for the action
- 6.11.6. Indicate the health risk; and
- 6.11.7. Provide specific instructions on what should be done with the recalled product.

Note: Where necessary, follow-up communication should be sent to those who fail to respond to the initial recall communication. This should be done within a reasonable time depending on the urgency of the recall.

6.12. POST RECALL PROCEDURES

The NMRA must be furnished with a report within a specified period (2 weeks) of the recall or withdrawal being instituted. The report should contain the following information:

- 6.12.1. Name of the product
- 6.12.2. Strength of the product
- 6.12.3. Pack size
- 6.12.4. Batch/ lot number
- 6.12.5. Nature of the defect
- 6.12.6. Action that was taken
- 6.12.7. Urgency of the action taken
- 6.12.8. Reason for the action
- 6.12.10. Indication of the health risk and reported clinical problems
- 6.12.11. Copies of all the recall correspondence; and
- 6.12.12. Steps taken to prevent re-occurrence of the problem
- 6.12.13. After termination of a recall and not later than 90 days after a recall has been instituted, a full reconciliation must be submitted.

A recall will be terminated when the NMRA and the recalling company are in agreement that the non-compliant product has been removed and proper disposal or correction has been made.



DEFINITIONS

Recall - means the removal of specific batch/batches of a medicinal product from the market for reasons relating to deficiencies in the quality, safety or efficacy.

Withdrawal - means the total withdrawal of a medicinal product from the market

Holder of a certificate of registration

- means a person in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality and safety and compliance with conditions of registration. This terminology will also include the agent/distributor of a drug.





RECALL ASSESSMENT FORM

- * The information below could be provided verbally but should be confirmed in writing within **3 working days**.

Recall information	Information by the holder of the certificate of registration/ Distributor/ parallel importer	Comments by NMRA (For official use only)
Origin of report		
1. Name of person/organization reporting the problem.		
2. Company		
3. Physical address		
4. Telephone Number.		
5. Facsimile number		
6. E-mail address		
7. Date of report		
8. Name of the recipient at the NMRA		
Product (Medicine) details		
1. Name of product affected		
2. Registration number		
3. Dosage form		
4. Strength		
5. Pack size/type		
6. Batch number and expiry date		
7. Manufacturer/holder of the certificate of registration, address and contact details		
8. Date manufactured		
9. Date released		
10. Total quantity prior to distribution		
11. Quantity released for distribution		



prior to the recall		
12. Date of distribution		
13. Local distribution (give full details and quantity)		
14.Overseas distribution (give full details and quantity)		
Nature of defect		
1.Source of problem (e.g patient/hospital/pharmacy/manufacture r, etc		
2. Details of problem		
3. Number of complaints received		
4. Name and address of any medicines regulatory affairs notified of the problem		
5.Action taken so far (If any) proposed and its urgency		
6. Type of hazard/health risk and assessment of risk to the user		
7. Proposed recall classification and type		
8. Other relevant information		





PART TWO:

**GUIDELINES ON GOOD MANUFACTURING
PRACTICE FOR MEDICINAL PRODUCTS FOR USE IN EAC**



ABBREVIATIONS AND ACRONYMS

AHU	-	Air Handling Unit
API	-	Active Pharmaceutical Ingredient
BAS	-	Building Automation System
BCG	-	Bacillus Calmette Guerin
BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
BMS	-	Building Management System
BOD	-	Biochemical Oxygen Demand
BP	-	British Pharmacopoeia
CAPA	-	Corrective Action and Preventive Action
COD	-	Chemical Oxygen Demand
CPPs	-	Critical Process Parameters
CQAs	-	Critical Quality Attributes
CTD	-	Common Technical Document
DNA	-	Deoxyribonucleic Acid
DQ	-	Design Qualification
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulation Harmonization project
eCTD	-	Electronic Common Technical Document
EMA	-	European Pharmaceutical products Agency
EN	-	European Norm
ETP	-	Effluent Treatment Plant
EU	-	European Union
FEAPM	-	Federation of East African Pharmaceutical Manufacturers
FMEA	-	Failure Modes Effects Analysis
FPP	-	Finished Pharmaceutical Product
GCP	-	Good Clinical Practice
GDP	-	Good Distribution Practice
GEP	-	Good Engineering Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
GxP	-	Good (x- variable replaced with manufacturing, clinical, laboratory, storage, distribution and review) Practice
HACCP	-	Hazard Analysis and Critical Control Point Harmonization
HAZOP	-	Hazard Operability Analysis
HEPA	-	High Efficiency Particulate Air
HPW	-	Highly Purified Water
HVAC	-	Heating Ventilation and Air Conditioning
ICH	-	International Conference on Harmonization of Technical
IQ	-	Installation Qualification
ISO	-	International Standard Organization



MA	-	Marketing Authorization
MAL	-	Material Air Lock
MRA	-	Medicines Regulatory Authority
MTC	-	Manufacturing Technology Committee
NEPAD	-	New Partnership for Africa's Development
NMRA	-	National Medicines Regulatory Authority
OQ	-	Operational Qualification
OSD	-	Oral Solid Dosage
PAL	-	Personnel Air Lock
pH	-	Power of Hydrogen
Ph. Eur	-	European Pharmacopoeia
Ph. Int.	-	International Pharmacopoeia
PIC/S	-	Pharmaceutical Inspection Cooperation Scheme
PP	-	Process Parameter
PQ	-	Performance Qualification
PQRI	-	Product Quality Research Institute
PQS	-	Pharmaceutical Quality System
PW	-	Purified Water
QA	-	Quality Assurance
QC	-	Quality Control
QRM	-	Quality Risk Management
QTPP	-	Quality Target Product Profile
		Requirements for Registration of Pharmaceuticals for Human Use
RMP	-	Risk Management Plan
SCADA	-	System Control and Data Acquisition
SOP	-	Standard Operating Procedure
TWG	-	Technical Working Group
UDAF	-	Unidirectional Air Flow
USP	-	United State Pharmacopoeia
VMP	-	Validation Master Plan
WFI	-	Water for Injection
WHO	-	World Health Organization



GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Active pharmaceutical ingredient: A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Authorized person: A person responsible for the release of batches of finished product for sale or distribution. Such a person is recognized by the national medicines regulatory framework as having the responsibility for ensuring that each of the finished products has been manufactured, tested and approved for release in compliance with the laws and regulations in force in each of the member states.

Batch (or lot): A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Batch numbering system: standard operating procedure describing the details of the batch numbering.

Batch records: All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bulk product: Any product that has completed all processing stages up to, but not including, final packaging.

Calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

Challenge tests/worst case: A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions.

Clean area: An area with defined environmental control of particulate and microbial contamination; constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Consignment (or delivery): The quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order.



A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Critical process: A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination: Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labeling.

Hazardous substance/product: A product or substance that may present a substantial risk of injury, to health or to the environment

In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Installation qualification: The performance of tests to ensure that the installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

Intermediate product: Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals: Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture: All operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

Manufacturer: A company that carries out at least one step of manufacture.

Manufacturing process: The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization (product license, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Master formula: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.



Master record: A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Medicinal product: Any medicine or similar product intended for human use, which is subject to control under national legislation in the manufacturing or importing State. (see also Pharmaceutical product)

Operational qualification: Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

Packaging: All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging material: Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

Quality assurance: See Chapter 1

Quality control: See Chapter 1

Quality unit (s): An organizational unit independent of production which fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in form of a separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or blending): The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.



Reprocessing: The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Returned product: Finished product sent back to the manufacturer.

Revalidation: Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

Specification: A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Standard operating procedure (SOP):

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Validation protocol (or plan): A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process - or a part thereof - for routine use.

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.



1. INTRODUCTION

The quality of medicinal products in the EAC region has always been a concern of National Medicine Regulatory Authorities. EAC NMRAs strive to ensure quality, safety and efficacy of human and veterinary medicines and other health care products through regulation and control of their production, importation, distribution and use.

Through the medicine regulation harmonization initiative in the EAC region, the GMP guidelines have been developed to ensure that medicinal products marketed in the Partner States meet uniform and acceptable quality, safety and efficacy.

The EAC Guide on Good Manufacturing Practices (GMP) is based on the World Health Organization (WHO) Good Manufacturing Practices guidelines in the WHO Technical Report Series No. 961, 2011. This guide also refers to the Pharmaceutical Inspection Convention Scheme (PIC/S) guide PE 009-9.

The national drug laws across all Partner States require medicinal products to be manufactured only by manufacturers whose activities are regularly inspected and authorized by the EAC NMRAs or competent inspectorates recognized by EAC NMRAs.

All manufacturers of medicinal products shall demonstrate, during a factory inspection, compliance with manufacturing principles specified in these guidelines. Local and foreign manufacturers of pharmaceutical products to be marketed in the EAC region shall be subjected to GMP conformity assessment following these guidelines and are required to meet an acceptable standard of GMP.

2. SCOPE

This guideline and its annexes shall be used as a basis for the inspection of medicinal products manufacturing facilities and as a standard to justify GMP status during the assessment of applications for manufacturing authorizations. The annexes provide details on specific areas which include; sterile preparations, biological medicinal products and vaccines for human use, computerized systems, water for pharmaceutical use, heating ventilation and air conditioning systems, qualification & validation, GMP for manufacture of active pharmaceutical ingredients, waste management for medicinal product manufacturers, quality risk management and authorized persons.

This guideline is applicable to all manufacturers (local and foreign) of finished pharmaceutical product formulations and active pharmaceutical ingredients manufactured and marketed in the EAC region for human use.

CHAPTER 1: QUALITY MANAGEMENT PRINCIPLE

The manufacturer's responsibility is to ensure the quality of medicinal products manufactured is fit for their intended use, comply with the requirements of market authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The achievement of this objective is the responsibility of management and requires the participation and commitment by staff in different departments and at all levels within the company, by the company's suppliers and distributors.



To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality assurance incorporating GMP and thus Quality control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems should be adequately resourced with competent personnel and suitable and sufficient premises, equipment and facilities.

1.1 The basic concepts of Quality assurance, GMP, and Quality control are inter-related aspects of Quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1.2 Quality management is defined as the aspect of management function that determines and implements the “quality policy” that is, the overall intention and direction of an organization as formally expressed and authorized by top management.

The basic elements of quality management are: An appropriate infrastructure or “quality system” encompassing the organizational structure, procedures, processes and resources; and systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

QUALITY ASSURANCE

1.3 “Quality assurance” is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

- (a) Medicinal products are designed and developed in a way that takes account of the requirements of GMP, GLP and GCP;
- (b) Production and control operations are clearly specified in a written form and GMP requirements are adopted;
- (c) Managerial responsibilities are clearly specified in job descriptions;
- (d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) All necessary controls on starting materials, intermediate products, and bulk products and any other in-process controls, calibrations, and validations are carried out;
- (f) The finished product is correctly processed and checked, according to the defined procedures;



- (g) Medicinal products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products;
 - (h) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
 - (i) There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
 - (j) Deviations are reported, investigated and recorded;
 - (k) There is a system for approving changes that may have an impact on product quality;
 - (l) Regular evaluation of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement;
 - (m) And there is a system for quality risk management (QRM);
- and as required by the marketing authorization and product specifications. GMP rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers. The basic requirements of GMP are that:
- (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing medicinal products of the required quality that comply with their specifications;
 - (b) critical steps of manufacturing processes and any significant changes made to the processes are validated;
 - (c) all necessary facilities are provided, including:
 - (i) appropriately qualified and trained personnel;
 - (ii) adequate premises and space;
 - (iii) suitable equipment and services;
 - (iv) correct materials, containers, and labels;
 - (v) approved procedures and instructions;
 - (vi) suitable storage and transport, and;

GOOD MANUFACTURING PRACTICES (GMP)

- 1.4 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use



- (vii) adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management.
- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply;
- (j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent recurrence.

QUALITY CONTROL

1.5 Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are neither released for use, nor for sale or supply, until their quality has been judged to be satisfactory. Quality control should not be confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

Each manufacturer should have a quality control department. The independence of quality control from production is considered fundamental. The quality control department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

- (a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions



- for GMP purposes.
- (b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
- (c) Test methods must be well documented and validated.
- (d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting, and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
- (e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labeled.
- (f) Records must be made of the results of inspecting and testing starting materials, intermediate, bulk, and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.
- (g) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from the production department
- (h) together with the authorized person from the quality control department. Sufficient reference samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.
- 1.6 The quality control department as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 1.7 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.
- 1.8 Quality control personnel must have access to production areas for sampling and investigation as appropriate.



PRODUCT QUALITY REVIEW

1.9 Regular, periodic or rolling quality reviews of all medicinal products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

- (a) review of starting materials and packaging materials used for the product, especially those from new sources;
- (b) a review of critical in-process controls and finished product results;
- (c) a review of all batches that failed to meet established specification(s) and their investigation;
- (d) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant corrective and preventive actions taken;
- (e) a review of all changes made to the processes or analytical methods;
- (f) a review of dossier variations submitted, granted or refused;
- (g) a review of the results of the stability monitoring programme and any adverse trends;
- (h) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;

- (i) a review of adequacy of any other previous corrective actions on product process or equipment;
- (j) for new dossiers and variations to the dossiers, a review of post-marketing commitments;
- (k) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and
- (l) a review of technical agreements to ensure that they are up to date.

The manufacturer and marketing authorization holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented.

Agreed corrective and preventive actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures should be verified during self-inspection.

Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective



responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

QUALITY RISK MANAGEMENT

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a pharmaceutical product. It can both be applied proactively and retrospectively.

The quality risk management system should ensure that: evaluation of the risk is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

SANITATION AND HYGIENE

A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For hygiene, please refer to chapter 2, "Personnel", and for sanitation to chapter 3, "Premises".)

CHAPTER 2: PERSONNEL

PRINCIPLE

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded.

GENERAL

- 2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- 2.2 The manufacturer must have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.
- 2.3 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including



hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

- (a) Pharmacy
- (b) pharmaceutical sciences and technology
- (c) chemistry (analytical or organic) or biochemistry,
- (d) chemical engineering,
- (e) microbiology

- 2.4 Steps should be taken to prevent unauthorized people from entering production, storage, and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

The education for head of production should include at least bachelor in any of the following:

KEY PERSONNEL

- 2.5 Key personnel include the head of production, the head of the quality unit; the head of Quality Assurance, the head of quality control, and the authorized person(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

- (a) Pharmacy
- (b) pharmaceutical sciences and technology,
- (c) chemistry (analytical or organic) or biochemistry,
- (d) chemical engineering,

The education for head of quality unit should include at least bachelor in any of the following:

- 2.6 Key personnel responsible for supervising the manufacture and quality unit including quality assurance and quality control for the manufacture of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by the partner states drug legislations. Their education should include the study of an appropriate combination of at least bachelors in:

- (a) Pharmacy
- (b) pharmaceutical sciences and technology,
- (c) chemistry (analytical or organic) or biochemistry,

The education for head of quality control should include at least bachelor in any of the following:

- (a) Pharmacy
- (b) pharmaceutical sciences and technology,
- (c) chemistry (analytical or organic) or biochemistry,
- (d) microbiology

- 2.7 They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a



- preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.
- 2.8 The heads of the production and quality control departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:
- (a) the authorization of written procedures and other documents, including amendments;
 - (b) the monitoring and control of the manufacturing environment;
 - (c) plant hygiene;
 - (d) process validation and calibration of analytical apparatus;
 - (e) training, including the application and principles of quality assurance;
 - (f) the approval and monitoring of suppliers of materials;
 - (g) the approval and monitoring of contract manufacturers;
 - (h) the designation and monitoring of storage conditions for materials and products;
 - (i) the performance and evaluation of in process controls
 - (j) the retention of records;
 - (k) the monitoring of compliance with GMP requirements;
- (l) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.
- 2.9 The head of the production department generally has the following responsibilities:
- (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
 - (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
 - (c) to ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;
 - (d) to check the maintenance of the department, premises, and equipment;
 - (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
 - (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.
- 2.10 The head of the quality unit including quality assurance and quality control department generally has the following responsibilities:
- (a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
 - (b) to evaluate batch records;



- (c) to ensure that all necessary testing is carried out;
 - (d) to approve sampling instructions, specifications, test methods, and other quality control procedures;
 - (e) to approve and monitor analyses carried out under contract;
 - (f) to check the maintenance of the department, premises and equipment;
 - (g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;
 - (h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need;
 - (i) establishment, implementation and maintenance of the quality system;
 - (j) supervision of regular internal audits or self-inspections;
 - (k) participation in external audits (vendor audits);
 - (l) participation in validation programmes.
- assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.
- 2.13 Personnel working in areas where contamination is a hazard, e.g., clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled should be given specific training.
- 2.14 The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.
- 2.15 Visitors or untrained personnel should preferably not be taken to production and quality control areas. If this is unavoidable they should be given relevant information in advance (particularly about personnel hygiene) and the prescribed protective clothing. They should be closely supervised.
- 2.16 Consultants and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

TRAINING

2.11 The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.12 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties



PERSONAL HYGIENE

- 2.17 All personnel, prior or and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
- 2.18 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.
- 2.19 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.
- 2.20 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment, or personnel) that they consider may adversely affect the products.
- 2.21 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.
- 2.22 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- 2.23 Eating, drinking, smoking, chewing, and storage of plants, food, drinks, smoking material, and personal medicines should not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.
- 2.24 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees - e.g., contractors' employees, visitors, senior managers, and inspectors.
- 2.25 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the guidelines under annexes.

CHAPTER 3: PREMISES

PRINCIPLE

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the



risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

GENERAL

- 3.1 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 3.2 Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation.
- 3.3 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- 3.4 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures and records should be maintained.
- 3.5 Electrical supply, lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- 3.6 Premises should be designed and equipped so as to provide maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

PRODUCTION AREA

- 3.7 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated, separate and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g., penicillins, cephalosporins) or biological preparations (e.g., live microorganisms). The production of certain additional products, such as certain antibiotics, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.
- 3.8 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations, materials flow, personnel movement and to the requisite cleanliness levels.



- 3.9 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.
- 3.10 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.
- 3.11 Pipe work, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- 3.12 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.
- 3.13 Production areas should be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.
- 3.14 Where dust is generated (e.g. during sampling, weighing, mixing, processing operations and packaging of powders) measures should be taken to avoid cross contamination and facilitate cleaning.
- 3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

STORAGE AREAS

- 3.17 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned, or recalled products.
- 3.18 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry, sufficiently lit and maintained within acceptable temperature limits.



Where special storage conditions are required (e.g., temperature, humidity) these should be provided. The conditions should be controlled, monitored and records maintained.

should be paid to sampling, the safe and secure storage of these materials.

WEIGHING AREAS

3.19 Receiving and dispatch bays should be separate and protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

3.25 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

QUALITY CONTROL AREAS

3.20 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

3.26 Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

3.21 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), and records.

3.22 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

3.28 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

3.23 Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

3.24 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling, and special attention



- 3.29 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors, or where it is necessary to isolate the instruments.

ANCILLARY AREAS

- 3.30 Rest and refreshment rooms should be separate from other areas.
- 3.31 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.
- 3.32 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

CHAPTER 4: EQUIPMENT PRINCIPLE

The layout, design and location of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

GENERAL

- 4.1 Manufacturing equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.
- 4.2 Repairs and maintenance operations should not present any hazard to the quality of the products.
- 4.3 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in clean and dry condition.
- 4.4 Non-dedicated equipment should be cleaned according to validated cleaning procedures between productions of different pharmaceutical products to avoid cross contamination.
- 4.5 Cleaning and drying equipment should be chosen and used so as not to be a source of contamination.
- 4.6 Equipment should be installed in such a way as to minimize any risk of error or of contamination.
- 4.7 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.
- 4.8 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is



- open, precautions should be taken to minimize contamination.
- 4.9 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated and checked at defined intervals using appropriate methods. Adequate records of such tests should be maintained.
- 4.10 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on the equipment.
- 4.11 Current drawings of critical equipment and support systems should be maintained.
- 4.12 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.
- 4.13 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 4.14 Water for pharmaceutical use (PW, WFI) and other water pipes should be sanitized, according to written procedures that detail the action limits for microbial contamination and the measures to be taken.
- 4.15 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 4.16 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

CHAPTER 5: DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. It ensures the availability of data needed for validation, review and statistical analysis. Documents must be free from errors and available in writing. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.



GENERAL

- 5.1 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.
- 5.2 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.
- 5.3 Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
- 5.4 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specified period of time
- 5.5 Where documents require the entry of data, these entries should be clear, legible, and indelible. Sufficient space should be provided for such entries.
- 5.6 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
- 5.7 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.
- 5.8 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.



LABELS

- 5.9 Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example: quarantined, accepted, rejected, or clean).
- 5.10 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:
- (a) the name of the drug product;
 - (b) a list of the active ingredients (if applicable, with the International Non-proprietary Names), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight, or volume;
 - (c) the batch number assigned by the manufacturer;
 - (d) the expiry date in an uncoded form;
 - (e) any special storage conditions or handling precautions that may be necessary;
 - (f) directions for use, and warnings and precautions that may be necessary; and
 - (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.
- 5.11 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

DOCUMENTS REQUIRED SPECIFICATIONS AND TESTING PROCEDURES

- 5.12 There should be appropriately approved and dated specifications and testing procedures for identity, content, purity, and quality for starting and packaging materials, and finished products; where appropriate, they should also be available for intermediate and bulk products. Specifications for water, solvents, and reagents (e.g., acids and bases) used in production should be included.
- 5.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.
- 5.14 Each specification and test procedure should be approved and maintained by the quality control unit.
- 5.15 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.
- 5.16 Pharmacopoeias, reference standards, reference spectra, and other reference materials should be available in the quality control laboratory.



SPECIFICATIONS FOR STARTING AND PACKAGING MATERIALS

- 5.17 Specifications for starting and primary or printed packaging materials should provide, if applicable description of the materials, including:
- the designated name (if applicable, the International Nonproprietary Name) and internal code reference;
 - the reference, if any, to a pharmacopoeial monograph;
 - qualitative and quantitative requirements with acceptance limits.

Depending on the company's practices other data may be added to the specifications such as:

- the approved supplier;
- a specimen of printed materials;
- directions for sampling and testing, or a reference to procedures;
- storage conditions and precautions;
- the maximum period of storage before re-examination.

Packaging material should conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for defects as well as for the correctness of identity markings.

- 5.18 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

SPECIFICATIONS FOR INTERMEDIATE AND BULK PRODUCTS

- 5.19 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

SPECIFICATIONS FOR FINISHED PRODUCTS

- 5.20 Specifications for finished products should include:
- the designated name of the product and the code reference where applicable;
 - the designated name(s) of the active ingredient(s) (if applicable, the International Nonproprietary Name(s));
 - the formula or a reference to the formula;
 - a description of the dosage form and package details;
 - directions for sampling and testing or a reference to procedures;
 - the qualitative and quantitative requirements, with acceptance limits;
 - the storage conditions and precautions, where applicable; and
 - the shelf-life.

MASTER FORMULAE AND PROCESSING INSTRUCTIONS

- 5.21 A formally approved master formula should exist for each product and batch size to be manufactured.

**5.22 The master formula should include:**

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product, and batch size;
- (c) a list of all starting materials to be used (if applicable, with the International Nonproprietary Names), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

5.23 The processing Instructions should include:

- (a) a statement of the processing location and the principal equipment to be used;
- (b) the methods, or reference to the methods, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing;
- (c) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (d) the instructions for any in-process controls with their limits;

- (e) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
- (f) any special precautions to be observed.

PACKAGING INSTRUCTIONS**5.24 There should be formally approved packaging instructions for each product pack size and type. These should normally include, or make reference to the following:**

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength, and method of application where applicable;
- (c) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after operations ;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;



- (h) details of in-process controls with instructions for sampling and acceptance limits.

BATCH PROCESSING RECORDS

5.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

5.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

5.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

- (a) the name of the product;
- (b) the number of the batch being manufactured;
- (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
- (d) the name of the person responsible for each stage of production;
- (e) the initials of the operator(s) of different significant steps of

- (f) production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing); the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
- (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

BATCH PACKAGING RECORDS

5.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

5.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment



is clean and suitable for use. These checks should be recorded.

5.30 The following information should be recorded at the time each action is taken and, after completion, the date and the person responsible should be clearly identified by signature or electronic password:

- (a) the name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained, and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing approval of the printing, the batch number, expiry date, and any additional overprinting;

- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

PROCEDURES (SOPS) AND RECORDS RECEIPTS

5.31 There should be written standard procedures and records for the receipt of each delivery of each starting material and primary and printed packaging material.

5.32 The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers;
- (b) the "in-house" name and/or code of material if different from (a);
- (c) the date of receipt;
- (d) the supplier's name and, if possible, manufacturer's name;
- (e) the manufacturer's batch or reference number;
- (f) the total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e.g., state of the containers).



5.33 There should be written standard operating procedures for the internal labeling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

SAMPLING

5.34 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

5.35 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- (d) the amount(s) of sample(s) to be taken;
- (e) instructions for any required subdivision of the sample;
- (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling;
- (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

TESTING

5.36 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

5.37 Analysis records should include at least the following data:

- (a) the name of the material or product and, where applicable, dosage form;
- (b) the batch number and, where appropriate, the manufacturer and/or supplier;
- (c) references to the relevant specifications and testing procedures;
- (d) test results, including observations and calculations, and reference to any specifications (limits);
- (e) dates and reference number of testing;
- (f) the initials of the persons who performed the testing;
- (g) the dates and initials of the persons who verified the testing and the calculations, where appropriate;
- (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

OTHERS

5.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.



- 5.39 The standard operating procedure for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.
- 5.40 Batch-number allocation should be immediately recorded, e.g., in a logbook. The record should include date of allocation, product identity, and size of batch.
- 5.41 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.
- 5.42 Records should be maintained for the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.
- 5.43 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:
- Validation
 - equipment assembly and qualification
 - analytical apparatus and calibration;
 - maintenance, cleaning, and sanitization;
 - personnel matters including qualification, training, clothing, and hygiene;
 - environmental monitoring;
 - pest control;
 - complaints;
 - recalls;
 - returns.
- 5.44 Logbooks should be kept with major and critical equipment and should record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.
- 5.45 Clear standard operating procedures should be available for major items of manufacturing and test equipment and placed in close proximity to the equipment.
- 5.46 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.
- 5.47 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used and facilities to be cleaned. Such written procedures should be followed.

CHAPTER 6: GOOD PRACTICES IN PRODUCTION

PRINCIPLE

Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.



GENERAL

- 6.1 Production should be performed and supervised by competent people.
- 6.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded. Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labeling materials.
- 6.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure; the authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.
- 6.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 6.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.
- 6.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms and packaging lines used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and the batch number. Where applicable, this indication should also mention the stage of production.
- 6.7 Access to production premises should be restricted to authorized personnel.
- 6.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.
- 6.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

PREVENTION OF CROSS-CONTAMINATION AND BACTERIAL CONTAMINATION IN PRODUCTION

- 6.10 When dry materials and products are used in production, special pre-cautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g supply and extraction of air of suitable quality)
- 6.11 Contamination of a starting material or of a product by another



- material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.
- 6.12 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:
- (a) production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals),
 - (b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
 - (c) providing appropriate airlocks, pressure differentials, and air extraction;
 - (d) minimizing the risk of contamination caused by recirculation or re-entry
- (e) of untreated or insufficiently treated air;
 - (f) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
 - (g) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
 - (h) using a "closed system" of production;
 - (i) testing for residues;
 - (i) using cleanliness status labels on equipment.
- 6.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.
- 6.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g for microbiological monitoring and particulate matter where appropriate).
- 6.15 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g food grade) to minimize health risks.
- 6.16 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.



VALIDATION

- 6.17 Validation studies should reinforce Good Manufacturing Practices and be conducted in accordance with defined procedures. Results and conclusions should be recorded.
- 6.18 Whenever a new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.
- 6.19 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.
- 6.20 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

STARTING MATERIALS

- 6.21 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.
- 6.22 Starting materials should be purchased only from suppliers named in the relevant specification and, where possible, directly from the producer. It is also recommended that the

specifications established by the manufacturer for the starting materials be discussed and agreed upon with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labeling, and packaging requirements as well as complaints and rejection procedures, are discussed and agreed upon between the manufacturer and the supplier.

- 6.23 For each consignment, the containers should be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.
- 6.24 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed data. Where additional labels are attached to containers, the original information should not be lost.
- 6.25 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.
- 6.26 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing, and release.
- 6.27 Starting materials in the storage area should be appropriately



labeled. Labels should bear at least the following information:

- (a) the designated name of the product and the internal code reference where applicable;
- (b) the batch number(s) given by the supplier and on receipt by the manufacturer, if any;
- (c) where appropriate, the status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled);
- (d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerized storage systems are used, not all of the above information need be in a legible form on the label.

- 6.28 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.
- 6.29 Only starting materials released by the quality control department and within their shelf-life should be used.
- 6.30 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.
- 6.31 Each dispensed material and its weight or volume should be independently checked and the check recorded.

6.32 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

6.33 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

6.34 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expiry, first-out rule.

PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS

6.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels, or documents not required for the current operation.

6.36 Intermediate and bulk products should be kept under appropriate conditions.

6.37 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

6.38 Any necessary in-process controls and environmental controls should be carried out and recorded.



- 6.39 Means should be instituted of indicating failures of equipment or of services (e.g., water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified.
- 6.40 Time limits for storage of equipment after cleaning and before use should be stated and based on data.
- 6.41 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- 6.42 Any significant deviation from the expected yield should be recorded and investigated.
- 6.43 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.
- 6.46 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 6.47 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

PACKAGING OPERATIONS

PACKAGING MATERIALS

- 6.44 The purchase, handling, and control of primary and printed packaging materials shall be as for starting materials.
- 6.45 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.
- 6.48 When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.
- 6.49 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used and not required for the current operation. The line clearance should be performed according to an appropriate procedure, checklist and recorded.



- 6.50 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 6.51 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.
- 6.52 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- 6.53 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.
- 6.54 The correct performance of any printing (for example of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.
- 6.55 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.
- 6.56 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.
- 6.57 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 6.58 On-line control of the product during packaging should include at least checks on:
- (a) the general appearance of the packages;
 - (b) whether the packages are complete;
 - (c) whether the correct products and packaging materials are used;
 - (d) whether any overprinting is correct;
 - (e) the correct functioning of line monitors.
- Samples taken away from the packaging line should not be returned.
- 6.59 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation, and approval by authorized personnel. A detailed record should be kept of this operation.



- 6.60 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- 6.61 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock
- 6.65 The reprocessing of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number.
- 6.66 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

FINISHED PRODUCTS

- 6.62 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.
- 6.63 The evaluation of finished products and the documentation necessary for release of a product for sale are described in **Chapter 7, "Good practices in quality control"**.
- 6.67 The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

REJECTED, RECOVERED REPROCESSED AND RETURNED MATERIALS

- 6.64 Rejected materials and products should be clearly marked as such
- 6.68 Products returned from the market should be destroyed unless it is certain that their quality is



satisfactory; they may be considered for resale, re-labelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

WASTE MATERIALS

- 6.69 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.
- 6.70 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

MISCELLANEOUS

- 6.71 Rodenticides, insecticides, fumigating agents, and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials, or finished products.

CHAPTER 7: GOOD PRACTICES IN QUALITY CONTROL

PRINCIPLE

Quality control is concerned with sampling, specifications, and testing as well as with the organization, documentation, and release procedures that ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of Quality control.

GENERAL

- 7.1 Each holder of manufacturing authorization should have a Quality Control Department. This department should be independent from other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be



available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

- 7.2 The principle duties of the head of Quality Control and the Quality Control department as a whole are summarized in Chapter 1. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

DOCUMENTATION

- 7.3 Laboratory documentation should follow the principles given in chapter 5. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department.

- Specifications;
- Sampling procedures;
- Testing procedures and records (including analytical worksheets and/or laboratory notebooks)
- Analytical reports and/or certificates;
- Data from environmental monitoring, where required;
- Validation records of test methods, where applicable;
- Procedures for and record for calibration of instruments and maintenance of equipment.

- 7.4 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

- 7.5 For some kinds of data (e.g. analytical test results, yields, environmental controls) it is

recommended that records be kept in a manner permitting trend evaluation.

- 7.6 In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

SAMPLING

- 7.7 The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the quantity of sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials
- the storage conditions
- instructions for the cleaning and storage of sampling equipment.

- 7.8 Reference samples should be representative of the batch of materials or products from which they are taken.

- 7.9 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If



exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of starting materials (other than solvents, gases and water) should be retained for at least one year beyond the expiry date of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least two full examination.

CONTROL OF STARTING MATERIALS AND INTERMEDIATE, BULK PRODUCTS

- 7.10 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.
- 7.11 Samples should be representative of the batches of material from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).
- 7.12 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

- 7.13 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.
- 7.14 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.
- 7.15 Each sample container should bear a label indicating:
- (a) the name of the sampled material;
 - (b) the batch or lot number;
 - (c) the number of the container from which the sample has been taken;
 - (d) the number of the sample
 - (e) the signature of the person who has taken the sample; and
 - (f) the date of sampling.

TEST REQUIREMENTS STARTING AND PACKAGING MATERIALS

- 7.16 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.
- 7.17 An identity test should be conducted on a sample from each container of starting material.



7.18 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 10.7 and 10.8) and through on-site audits of the supplier's capabilities. (This does not affect section 7.18). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

- (a) identification of the issuing supplier, signature of the competent official, and statement of his or her qualifications;
- (b) the name and batch number of the material tested;
- (c) a statement of specifications and methods used; and
- (d) a statement of test results obtained and the date of testing.

Each batch (lot) of printed packaging materials must be examined following receipt

IN-PROCESS CONTROL

7.19 In-process control records should be maintained and form a part of the batch records (see section 6.24).

FINISHED PRODUCTS

7.20 For each batch of drug product, there should be an appropriate laboratory determination of

satisfactory conformity to its finished product specification prior to release.

7.21 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

BATCH RECORD REVIEW

7.22 Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

7.23 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

STABILITY STUDIES

7.24 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of



- any stability issue (e.g. changes in levels of impurities, or dissolution profile) associated with the formulation in the marketed package.
- 7.25 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions.
- 7.26 This mainly applies to the medicinal product in the package, in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/ or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.
- 7.27 The on-going stability programme should be described in a written protocol following the general rules of Chapter 5 and results formalised as a report. The equipment used for the on-going stability programme
- (stability chambers among others) should be qualified and maintained.
- 7.28 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.
- 7.29 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.
- 7.30 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written



- agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.
- 7.31 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 9 of the GMP Guide and in consultation with the NMRA in the member state.
- 7.32 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.
- 7.33 The quality control department should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.
- 7.34 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- 7.35 A written programme for ongoing stability determination should be developed and implemented to include elements such as:
- (a) a complete description of the drug involved in the study;
 - (b) the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - (c) provision for the inclusion of a sufficient number of batches;
 - (d) the testing schedule for each drug;
 - (e) provision for special storage conditions;
 - (f) provision for adequate sample retention; and
 - (g) a summary of all the data generated, including the evaluation and the conclusions of the study.
- 7.36 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

REAGENTS AND CULTURE MEDIA

- 7.37 All reagents and culture media should be recorded upon receipt or preparation.
- 7.38 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.



7.39 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

REFERENCE STANDARDS

7.40 Reference standards may be available in the form of official reference standards. Official reference standards are those obtained from official recognized pharmacopeia source for example B.P, Ph. Eur, Ph. Int., USP

7.41 Reference standards prepared by the producer should be tested, released, and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

7.42 Reference standards should be properly labelled with at least the following information:

- (a) name of the material;
- (b) batch or lot number and control number;
- (c) date of preparation;
- (d) shelf-life;
- (e) potency;
- (f) storage conditions.

7.43 Official reference standards should be used only for the purpose described in the appropriate monograph.

7.44 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

7.45 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

7.46 All reference standards should be stored and used in a manner that will not adversely affect their quality.

CHAPTER 8: CONTRACT PRODUCTION AND ANALYSIS

PRINCIPLE

Contract production and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility.

GENERAL

8.1 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.



8.2 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.3 The contract should permit the contract giver to audit the facilities of the contract acceptor.

8.4 In the case of contract analysis, the final approval for release must be given by the authorized person(s) of the contract giver.

THE CONTRACT GIVER

8.5 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

8.6 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.

8.7 The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their

specifications or that the product has been released by the authorized person(s).

THE CONTRACT ACCEPTER

8.8 The contract acceptor must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

8.9 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

8.10 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

THE CONTRACT

8.11 A contract should be drawn up between the contract giver and the contract acceptor that specifies their respective responsibilities relating to the manufacture and control of the product. Technical



- aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.
- 8.12 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.
- 8.13 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.
- 8.14 Manufacturing, analytical, and distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.
- 8.15 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.
- 8.16 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.
- 8.17 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

CHAPTER 9: COMPLAINTS HANDLING AND PRODUCT RECALL

PRINCIPLE

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market complaints.

- 9.1 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter



- should be made aware of any complaint, investigation, or recall.
- 9.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 9.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the study of such problems.
- 9.4 If product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.
- 9.5 Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions.
- 9.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 9.7 All the decisions and measures taken as a result of a complaint
- should be recorded and referenced to the corresponding batch records.
- 9.8 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.
- 9.9 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.
- ### **PRODUCT RECALL**
- 9.10 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of sales and marketing department. If this person is different from the authorized person, the latter should be made aware of any recall operation.
- 9.11 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of an hospital or pharmacy or any authorized drug outlet.
- 9.12 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product



because it is, or is suspected of being, defective.

- 9.13 The distribution records should be readily available to a person responsible for recalls, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.
- 9.14 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including reconciliation between the delivered and recovered quantities of the products.
- 9.15 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.
- 9.16 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

CHAPTER 10: SELF - INSPECTION, QUALITY AUDITS, SUPPLIER AUDITS AND APPROVALS

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be

designed to detect any Shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

- 10.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:
- (a) personnel;
 - (b) premises including personnel facilities;
 - (c) maintenance of buildings and equipment;
 - (d) storage of starting materials and finished products;
 - (e) equipment;
 - (f) production and in-process controls;
 - (g) QC;
 - (h) documentation;
 - (i) sanitation and hygiene;
 - (j) validation and revalidation programmes;
 - (k) calibration of instruments or measurement systems;
 - (l) recall procedures;
 - (m) complaints management;
 - (n) labels control;



- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

- 10.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

- 10.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

- 10.5 A report should be made at the completion of a self-inspection. The report should include:
 - (a) self-inspection findings;
 - (b) evaluation and conclusions; and
 - (c) recommended corrective actions.

Follow-up action

- 10.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

- 10.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment

of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 8, "Contract production and analysis").

Vendors'/Suppliers' audits and approval

- 10.8 The person responsible for QC should have responsibility together with other relevant departments for approving vendor/suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 10.9 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a vendor's/supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

6. REFERENCES

- a) WHO TRS GMP Guide: Basic requirements 2011
- b) Guide to Good Manufacturing Practices Part 1: PEE-009-9 September 2009, Pharmaceutical Inspection Cooperation Scheme (PIC/S)



7. REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	17th April 2014	EAC TWG GMP Members	All	First approved version to be issued	REF: EAC/SC/ DECISION---- --/17TH APRIL 2014

8. LIST OF ANNEXES

- Annex 1:** Manufacture of Sterile Medicinal Products
- Annex 2:** Manufacture of Biological Medicinal Products for Human Use
- Annex 3:** Qualification and Validation
- Annex 4:** Computerized Systems
- Annex 5:** Water for Pharmaceutical Use
- Annex 6:** Heating, Ventilation and Air Conditioning Systems for Non-sterile Pharmaceutical Dosage Forms
- Annex 7:** Authorized Persons
- Annex 8:** Quality Risk Management
- Annex 9:** GMP for Manufacture of Active Pharmaceutical Ingredients
- Annex 10:** Waste Management for medicinal product manufacture



ANNEX 1: MANUFACTURE OF STERILE MEDICINAL PRODUCTS

PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc.

GENERAL

1. The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.
2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. The "at rest" state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working. The "in operation" and "at rest" states should be defined for each clean room or suite of clean rooms.

For the manufacture of sterile medicinal products 4 grades can be distinguished.

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.



Grade B: For aseptic preparation and filling, this is the background environment for grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

Grade	At rest ^(b)		In operation ^(b)	
	Maximum permitted number of particles/m ³ equal to or above ^(a)			
	0.5µm ^(d)	5µm	0.5µm ^(d)	5µm
A	3,500	1 ^(e)	3,500	1 ^(e)
B ^(c)	3,500	1 ^(e)	350,000	2,000
C ^(c)	350,000	2,000	3,500,000	20,000
D ^(c)	3,500,000	20,000	not defined ^(f)	not defined ^(f)
0				

Notes:

- (a) Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated. A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas.
- (b) The particulate conditions given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. The particulate conditions for grade A “in operation” given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standard at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.
- (c) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as HEPA for grades A, B and C.
- (d) The guidance given for the maximum permitted number of particles in the “at rest” and “in operation” conditions correspond approximately to the cleanliness classes in the EN/ISO 14644-1 at a particle size of 0.5 µm.



- (e) These areas are expected to be completely free from particles of size greater than 5 micrometer. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle /m³. During the clean room qualification it should be shown that the areas can be maintained within the defined limits.
- (f) The requirements and limits will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below (see also para. 11 and 12):

Grade	Examples of operations for terminally <u>sterilised</u> products (see <u>para. 11</u>)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for terminally sterilized products (see <u>para. 12</u>)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

4. The areas should be monitored during operation in order to control the particulate cleanliness of the various grades.
5. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

**Recommended limits for microbiological monitoring of clean areas during operation:**

Grade	Recommended limits for microbial contamination ^(a)				
	Air sample cfu/m ³	Settle plates (diam. 90 mm), cfu/4 hours ^(b)	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers cfu/glove	
A	< 1	< 1	< 1	< 1	
B	10	5	5	5	
C	100	50	25	-	
D	200	100	50	-	

Notes:

- (a) These are average values.
- (b) Individual settle plates may be exposed for less than 4 hours.
6. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

ISOLATOR TECHNOLOGY

7. The utilization of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilization mechanisms.

The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognized that laminar air flow may not exist in the working zone of all such devices. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.

8. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitation of the isolator, the transfer process and isolator integrity.



9. Monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.

BLOW/FILL/SEAL TECHNOLOGY

10. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits "at rest" and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products for terminal sterilization should be installed in at least a grade D environment.

Because of this special technology particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning-in-place and sterilization-in-place, background clean room environment in which the equipment is located, operator training and clothing, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

TERMINALLY STERILIZED PRODUCTS

11. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization. Where there is unusual risk to the product because of microbial contamination, for example, because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels, preparation should be done in a grade C environment.

Filling of products for terminal sterilization should be done in at least a grade C environment.

Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

ASEPTIC PREPARATION

12. Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilization or filtration through a micro-organism-retaining filter later in



the process, should be done in a grade A environment with grade B background.

Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.

Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

PERSONNEL

13. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.

14. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

15. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

16. High standards of personnel hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person



17. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
18. Wristwatches, make-up and jewellery should not be worn in clean areas.
19. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.
20. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.

The description of clothing required for each grade is given below:

Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C: Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves

and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

21. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

PREMISES

22. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.



23. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.
24. False ceilings should be sealed to prevent contamination from the space above them.
25. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
26. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.
27. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the "at rest" state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.
28. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
29. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.
30. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person,



operation or machine to a zone of higher product risk.

31. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

EQUIPMENT

32. A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).
33. As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it should be carried out after complete reassembly wherever possible.
34. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.
35. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a

reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

36. All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

SANITATION

37. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.
38. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.
39. Fumigation of clean areas may be useful for reducing



microbiological contamination in inaccessible places.

PROCESSING

40. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.
41. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.
42. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with 95% confidence limit is acceptable. The manufacturer should establish alert and action limits. Any contamination should be investigated.
43. Care should be taken that any validation does not compromise the processes.
44. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.
45. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.



46. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
47. Containers and materials liable to generate fibres should be minimized in clean areas.
48. Where appropriate, measures should be taken to minimize the particulate contamination of the end product.
49. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.
50. The interval between the washing and drying and the sterilization of components, containers and equipment as well as between their sterilization and use should be minimized and subject to a time-limit appropriate to the storage conditions.
51. The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter should be minimized. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.
52. The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.
53. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases should be passed through micro-organism retentive filters.
54. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

STERILIZATION

55. All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilization is the method of choice. In any case, the sterilization process



- must be in accordance with the marketing and manufacturing authorizations.
56. Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
57. For effective sterilization the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
58. Validated loading patterns should be established for all sterilization processes.
59. Biological indicators should be considered as an additional method for monitoring the sterilization. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls.
- If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.
60. There should be a clear means of differentiating products which have not been sterilized from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, sterile.
61. Sterilization records should be available for each sterilization run. They should be approved as part of the batch release procedure.
- ### STERILIZATION BY HEAT
62. Each heat sterilization cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.
63. Chemical or biological indicators may also be used, but should not take the place of physical measurements.



64. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed.
65. After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

MOIST HEAT

66. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

67. The items to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilization. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.
68. Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

DRY HEAT

69. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

STERILIZATION BY RADIATION

70. Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally.



Ultraviolet irradiation is not normally an acceptable method of sterilization.

STERILIZATION WITH ETHYLENE OXIDE

71. During the sterilization procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
72. Biological indicators may be used as an additional control.
73. Validation procedures should ensure that the effects of variations in density of the packages are considered.
74. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to a irradiation and those which have not.
75. The total radiation dose should be administered within a predetermined time span.

76. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.
77. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.
78. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.
79. Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.



80. For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.
81. After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.
- FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILIZED IN THEIR FINAL CONTAINER**
82. Filtration alone is not considered sufficient when sterilization in the final container is possible. With regard to methods currently available, steam sterilization is to be preferred. If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasma's. Consideration should be given to complementing the filtration process with some degree of heat treatment.
83. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.
84. Fibre shedding characteristics of filters should be minimal.
85. The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences during routine manufacturing from this should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.
86. The same filter should not be used for more than one working day unless such use has been validated.
87. The filter should not affect the product by removal of ingredients from it or by release of substances into it.



FINISHING OF STERILE PRODUCTS

88. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.
89. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
90. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

QUALITY CONTROL

91. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.
92. In those cases where parametric release has been authorized, special attention should be paid to the validation and the monitoring of the entire manufacturing process.
93. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:
- a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;
 - b) for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.



ANNEX 2: MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

SCOPE

The regulatory procedures necessary to control biological products are in large part determined by the sources of products and methods of manufacture. Manufacturing procedures with the scope of these guidelines include:

- a. growth of strains of microorganisms and eukaryotic cells,
- b. extraction of substances from biological tissues, including human, animal and plant tissues (allergens),
- c. recombinant DNA (rDNA) techniques,
- d. hybridoma techniques,
- e. propagation of microorganisms in embryos or animals.

Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA) and diagnostic agents for in vitro use.

This guidance does not lay down detailed requirements for specific classes of biological products.

PRINCIPLE

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are

produced, controlled and administered make some particular precautions necessary. Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a great importance in the manufacture of biological medicinal products.

The special properties of biological medicinal products require careful consideration in any code of Good Manufacturing Practice and the development of this annex takes these points into account.

PERSONNEL

1. The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.



2. Personnel required to work in clean and aseptic areas should be selected with care, to ensure that they may be relied upon to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product microbiologically or otherwise. High standards of personal hygiene and cleanliness are essential. Staff should be instructed to report any conditions (e.g. diarrhea, coughs, infected skin or hair, wounds, fever of unknown origin) that may cause the shedding of abnormal numbers or types of organisms into the working environment. Health checks on personnel for such condition should be required before employment and periodically thereafter. Any changes in health status that could adversely affect the quality of the product shall preclude the person concerned from working in the production area.
3. Only the minimum number of personnel required should be presenting clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside these areas as far as possible.
4. During the working day, personnel shall not pass from areas where live microorganisms or animals are handled to premises where other products or organisms are handled unless clearly defined decontamination measures, including a change of clothing and shoes, are followed. Persons not concerned with the production process should not enter the production area except for essential purposes, and in that case they shall be supplied with sterile protective clothing.
5. The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.
6. The names and qualifications of those responsible for approving lot processing records (protocols) should be registered with the national control authority.
7. To ensure the manufacturing of high-quality products, personnel should be trained in good manufacturing and laboratory practices in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine.
8. Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.
9. All personnel engaged in production, maintenance, testing and animal care (all inspectors) should be vaccinated with appropriate vaccines and where appropriate, be submitted to regular testing for evidence of active tuberculosis.



Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with these agents.

10. Where BCG vaccines are being manufactured, access to production areas shall be restricted to staff who are carefully monitored by regular health checks. In the case of manufacture of products derived from human blood or plasma, vaccination of workers against hepatitis is recommended.

PREMISES AND EQUIPMENT

11. As a general principle, buildings must be located, designed constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories, operating rooms and all other rooms and buildings (including those for animals) that are used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom from dust, insects and vermin, can be maintained.
12. Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains shall be avoided whenever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily

cleanable traps and with breaks to prevent back-flow. The traps may contain electrically operated heating devices or other means for disinfection. Any floor channels should be open, shallow and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

13. Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production process, including those from personnel, shall be avoided.
14. Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise



- products. Premises should provide sufficient space to suit the operations carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the manufacture of biological substances is resumed. Areas used for processing animal tissue materials and microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.
15. If certain products are to be produced on a campaign basis, the layout and design of the premises and equipment shall permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.
16. Seed lots and cell banks used for the production of biological products should be stored separately from other material. Access should be restricted to authorized personnel.
17. Live organisms shall be handled in equipment that ensures that cultures are maintained in a pure state and are not contaminated during processing.
18. Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, if appropriate, sterilization and washing.
19. Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished. For *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium tetani*, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at a time.
20. Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.
21. All containers of biological substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination should be prevented by adoption of some or all of the following measures:
- processing and filling in segregated areas;
 - avoiding manufacture of different products at the same time, unless they are effectively segregated;



- containing material transfer by means of airlocks, air extraction, clothing change and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using “closed systems” of manufacture;
- taking care to prevent aerosol formation (especially by centrifugation and blending);
- excluding pathological specimens sent in for diagnosis from areas used for manufacturing biological substances;
- using containers that are sterilized or are of documented low “bioburden”.

22. Positive-pressure areas should be used to process sterile products, but negative pressure is acceptable in specific areas where pathogens are processed. In general, any organisms to be pathogenic should be handled within specifically designed areas under negative pressures, in accordance with containment requirements for the product concerned.

- a. Air-handling units should be dedicated to the processing area concerned. Air from operations involving pathogens shall not be re-circulated and, in the case of organisms in a group above Risk Group 2 (3), shall be exhausted through sterilizing filters that are regularly checked for performance.
- b. Specific decontamination systems should be considered for effluent

when infectious and potentially infectious materials are used for production.

- c. Pipe work, valves and vent filters shall be properly designed to facilitate cleaning and sterilization. Valves on fermentation vessels shall be completely steam-sterilizable. Air-vent filters shall be hydrophobic and shall be validated for their designated use.
- d. Small stocks of substances that have to be measured or weighed during the production process (e.g. buffers) may be kept in the production area, provided that they are not returned to the general stocks. Otherwise, dry materials used to formulate buffers, culture media, etc should be weighed and put into solution in a contained area outside the purification and aseptic areas in order to minimize contamination of the product.

ANIMAL QUARTERS AND CARE

23. Animals are used for the manufacture and control of a number of biological products. Animals shall be accommodated in separate buildings with self-contained ventilation systems. The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage. Provision shall also be made for animal inoculation rooms, which



shall be separate from the postmortem rooms. There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

24. The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in animal quarters must be provided with special clothing, changing facilities and showers. Where monkeys are used for the production or quality control of biological products, special consideration is required, as laid down in the revised Requirements for **Biological Substances No. 7 (Requirements for Polio-myelitis Vaccine (Oral)) (5)**.

PRODUCTION

25. Standard operating procedures shall be available and maintained up to date for all manufacturing operations.
- a. The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.
- b. Where sterilisation of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).
- c. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture of propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.
- d. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorization dossier. Scaling up of the process should not change this fundamental relationship.
- e. Seed lots and cell banks should be adequately characterised and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination or alteration.
- f. Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the



- establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.
- g. Evidence of the stability and recovery of the seeds and banks should be documented. Storage containers should be hermetically sealed, clearly labeled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.
- h. Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risks of total loss.
- i. All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.
- j. The growth promoting properties of culture media should be demonstrated.
- k. Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.
- l. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.
- m. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.
- n. Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.
- o. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.
- p. A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilized



or sanitized between batches. The use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilization method of columns should be defined.

LABELING

26. All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labeling (for example a capillary tube), it should be in a labeled package.

27. The information given on the label on the container and the label on the package shall be approved by the national control authority.

28. The label on the container shall show:-

- the name of the drug product;
- a list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume;
- the batch or final lot number assigned by the manufacturer;
- the expiry date;
- recommended storage conditions or handling precautions that may be necessary;
- directions for use, and warnings and precautions that may be necessary;
- the nature and amount of any

substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients;

- the name and address of the manufacturer or the company and/ or the person responsible for placing the drug on the market.

29. The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.

- a. The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.

Lot Processing Records (Protocols) And Distribution Records

30. Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.

31. A separate processing record should be prepared for each lot of biological product, and should include the following information:

- the name and dosage of the product;
- the date of manufacture;
- the lot identification number;
- the complete formulation of the



- lot, including identification of seed or starting materials;
- the batch number of each component used in the formulation;
 - the yield obtained at different stages of manufacture of the lot;
 - a duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
 - a record of all in-process control tests and of the results obtained;
 - a specimen of the label;
 - identification of packaging materials, containers and closures used;
 - a dated signature of the expert responsible for approving the manufacturing operations;
 - an analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority;
 - a record of the decision regarding the release or rejection of the lot by the quality-control department and, if the lot is rejected, a record of its disposal or utilization.
32. The records shall be of a type approved by the national control authority. They shall be retained for at least two years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by the national control authority.
- a. Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization

of all apparatus and materials used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

QUALITY CONTROL

33. The quality-assurance and/or quality-control department should have the following principal duties:
- to prepare detailed instructions for each test and analysis;
 - to ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;
 - to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
 - to release or reject raw materials and intermediate products, if necessary;
 - to release or reject packaging and labeling materials and the final containers in which drugs are to be placed;
 - to release or reject each lot of finished preparation;
 - to evaluate the adequacy of the conditions under which raw materials, intermediate products and finished biological preparations are stored;
 - to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
 - to establish expiry dates on the basis of the validity period related to specified storage conditions;
 - to establish and, when necessary,



- revise control procedures and specifications; and
 - to be responsible for the examination of returned preparations to determine whether such preparations should be released; reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.
34. A manufacture's quality-control laboratory shall be separated from the production area and ideally should be in a separate building. The control laboratory should be designed and equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, preparation of records and performance of the necessary tests.
- a. In-process controls play a special important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.
 - b. Performance of all qualitative and quantitative tests mentioned in the specifications for starting materials may be replaced by a system of certificates issued by the producer of the starting material, provided that:
 - there is a history of reliable production,
 - the producer is regularly audited, and
 - at least one specific identity test is conducted by the manufacturer of the final product.
 - c. Samples of intermediate and final products shall be retained in sufficient amount and under appropriate storage conditions to allow the repetition or confirmation of a batch control. However, reference samples of certain starting materials, e.g. components of culture media, need not necessarily be retained.
 - d. Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.
 - e. Special consideration needs to be given to the quality-control requirements arising from production of biological products by continuous culture.



ANNEX 3: QUALIFICATION AND VALIDATION

PRINCIPLE

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

PLANNING FOR VALIDATION

2. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.
3. The VMP should be a summary document which is brief, concise and clear.
4. The VMP should contain data on at least the following:
 - a) validation policy;
 - b) organizational structure of validation activities;
 - c) summary of facilities, systems, equipment and processes to be validated;
 - d) documentation format: the format to be used for protocols and reports;
 - e)

- f) change control;
- g) reference to existing documents.

5. In case of large projects, it may be necessary to create separate validation master plans.

DOCUMENTATION

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.
7. A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.
8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorization.

QUALIFICATION

Design qualification

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).



10. The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

11. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
12. IQ should include, but not be limited to the following:
- a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
 - b) collection and collation of supplier operating and working instructions and maintenance requirements;
 - c) calibration requirements;
 - d) verification of materials of construction.

Operational qualification

13. Operational qualification (OQ) should follow Installation qualification.
14. OQ should include, but not be limited to the following:
- a) tests that have been developed from knowledge of processes, systems and equipment;
 - b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.
15. The completion of a successful Operational qualification should allow the finalization of calibration,

operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal “release” of the facilities, systems and equipment.

Performance qualification

16. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.
17. PQ should include, but not be limited to the following:
- a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
 - b) tests to include a condition or set of conditions encompassing upper and lower operating limits.
18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

19. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.



PROCESS VALIDATION

General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and revalidation.
21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).
22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.
23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.
- (a) short description of the process;
(b) summary of the critical processing steps to be investigated;
(c) list of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
(d) finished product specifications for release;
(e) list of analytical methods, as appropriate;
(f) proposed in-process controls with acceptance criteria;
(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
(h) sampling plan;
(i) methods for recording and evaluating results
(j) functions and responsibilities;
(k) proposed timetable.
25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process.

Prospective validation

24. Prospective validation should include, but not be limited to the following:
26. Batches made for process validation should be the same size as the intended industrial scale batches.
27. If it is intended that validation batches be sold or supplied, the



conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorization.

Concurrent validation

28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
29. The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.
34. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
35. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

CLEANING VALIDATION

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
37. Validated analytical methods having sensitivity to detect residues or



contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing a "worst case" approach can be carried out which takes account of the critical issues.
40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.
41. "Test until clean" is not considered an appropriate alternative to cleaning validation.
42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

CHANGE CONTROL

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

REVALIDATION

45. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.



GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current EAC-GMP Guide, but which are used in this Annex, are given below.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Prospective Validation

Validation carried out before routine production of products intended for sale.



Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis

Method to assess and characterize the critical parameters in the functionality of an equipment or process.

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

System

A group of equipment with a common purpose.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.



ANNEX 4: COMPUTERIZED SYSTEMS

PRINCIPLE

The introduction of computerized systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the Guide. Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

PERSONNEL

1. It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilizes computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerized system.

VALIDATION

2. The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether it is prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer

system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

SYSTEM

3. Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.
4. A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.
5. The software is a critical component of a computerized system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.
6. The system should include, where appropriate, built-in checks of the correct entry and processing of data.
7. Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.



8. Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorized persons.
9. When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.
10. The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorized and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments (an "audit trail").
11. Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change. Such an alteration should only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.
12. For quality auditing purposes, it should be possible to obtain meaningful printed copies of electronically stored data.
13. Data should be secured by physical or electronic means against willful or accidental damage, and this in accordance with item 5.8 of the Guide. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.
14. Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.
15. There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them.



- For example, information required to effect a recall must be available at short notice.
16. The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.
17. A procedure should be established to record and analyze errors and to enable corrective action to be taken.
18. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency. (see chapter 8)
19. When the release of batches for sale or supply is carried out using a computerized system, the system should recognize that only an Authorized Person can release the batches and it should clearly identify and record the person releasing the batches.



ANNEX 5: WATER FOR PHARMACEUTICAL USE

1.1 Scopes

The guidance contained in this document is intended to provide information about the available specifications for water for pharmaceutical use (WPU), guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms, and to provide guidance on the good manufacturing practice (GMP) regarding the design, installation and operation of pharmaceutical water systems. Although the focus of this document is on water for pharmaceutical applications, the guidelines may also be relevant to other industrial or specific uses where the specifications and practices can be applied.

This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material. Note: This document does not cover waters for administration to patients in their formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

The guidance provided in this document can be used in whole or in part as appropriate to the application under consideration. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorization submitted to the national drug regulatory authority.

1.2 Background to water requirements and uses

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.

1.3 Applicable guides

In addition to the specific guidance provided in this document, the Bibliography lists some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

2. General requirements for pharmaceutical water systems

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for



planned preventive maintenance tasks, they need not be approved after implementation. Water sources and treated water should be monitored regularly for quality and for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results and any actions taken should be maintained for an appropriate length of time.

Where chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed to ensure that the sanitizing agent has been effectively removed.

3. Water quality specifications

3.1 General

The following requirements concern water processed stored and distributed in bulk form. They do not cover the specification of waters formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form waters.

Pharmacopoeial requirements for WPU are described in national and inter- national pharmacopoeias and limits for various contaminants are given. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

3.2 Drinking water

Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes softening, removal of specific ions, particle reduction and antimicrobial treatment. It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It is also common for public water-supply organizations to conduct tests and guarantee that the drinking-water delivered is of potable quality.

Drinking-water quality is covered by the WHO drinking-water guidelines, standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site to confirm that the quality meets the standards required for potable water.

3.3 Purified water

Purified water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.



3.4 Highly purified water

Highly purified water (HPW) should be prepared from potable water as minimum-quality feed-water. HPW is a unique specification for water found only in the European Pharmacopoeia. This grade of water must meet the same quality standard as water for injections (WFI) including the limit for endotoxins, but the water-treatment methods are not considered to be as reliable as distillation. HPW may be prepared by combinations of methods such as reverse osmosis, ultra filtration and deionization.

3.5 Water for injections

Water for injections (WFI) should be prepared from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

Certain pharmacopoeias place constraints upon the permitted purification techniques as part of the specification of the WFI. The International Pharmacopoeia and the European Pharmacopoeia, for example, allow only distillation as the final purification step.

3.6 Other grades of water

When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

4. Application of specific waters to processes and dosage forms

Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.

The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

HPW can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for WFI.

WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI should also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it should conform to the specification for WFI when condensed.



5. Water purification methods

5.1 General considerations

The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI (refer to section 3.5).

The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method:

- the water quality specification;
- the yield or efficiency of the purification system;
- feed-water quality and the variation over time (seasonal changes);
- the reliability and robustness of the water-treatment equipment in operation;
- the availability of water-treatment equipment on the market;
- the ability to adequately support and maintain the water purification equipment; and
- the operation costs.

The specifications for water purification equipment, storage and distribution systems should take into account the following:

- the risk of contamination from leachates from contact materials;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- configuration to avoid proliferation of microbiological organisms;

- tolerance to cleaning and sanitizing agents (thermal and chemical);
- the system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.

The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the space available for the installation;
- structural loadings on buildings;
- the provision of adequate access for maintenance; and
- the ability to safely handle regeneration and sanitization chemicals.

5.2 Production of drinking-water

Drinking-water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce potable drinking-water from a specific raw water source.

Typical processes employed at a user plant or by a water supply authority include:

- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
- iron (ferrous) removal;
- precipitation; and
- reduction of specific inorganic/organic materials.



The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking water quality changes significantly, the direct use of this water as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented.

Where drinking-water is derived from an "in-house" system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or its operation should not be made until a review has been completed and the change approved by the QA department.

Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, its use should ensure a turnover of the stored water sufficient to prevent stagnation. The drinking-water system is usually considered to be an "indirect impact system" and does not need to be qualified.

Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed

with appropriately protected vents, allow for visual inspection and for being drained and sanitized. Distribution pipe work should be able to be drained, or flushed, and sanitized.

Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back-flushing, chemical or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be maintained with continuous water flow to inhibit microbial growth.

5.3 Production of purified water

There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultra filtration and/or reverse osmosis processes are used. Distillation can also be used.

The following should be considered when configuring a water purification system:

- the feed-water quality and its variation over seasons;
- the required water-quality specification;
- the sequence of purification stages required;
- the energy consumption;
- the extent of pretreatment required to protect the final purification steps;
- performance optimization, including yield and efficiency of unit treatment- process steps;



- appropriately located sampling points designed in such a way as to avoid potential contamination; and
- unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

Ambient-temperature PW systems are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbiological control and sanitization. The following techniques should be considered:

- maintenance of flow through water-purification equipment at all times;
- control of temperature in the system by pipeline heat exchange or plant-room cooling to reduce the risk of microbial growth (guidance value <25°C);
- provision of ultraviolet disinfection;
- selection of water-treatment components that can be thermally sanitized; and/or
- application of chemical sanitization (including agents such as ozone).

5.4 Production of highly purified water

There are no prescribed methods for the production of HPW in any major pharmacopoeia, including the European Pharmacopoeia. Any appropriate qualified purification technique or sequence of techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. The guidance provided in section 5.3 for PW is equally applicable to HPW.

5.5 Production of water for injections

The pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. Distillation is the preferred technique; it is considered a more robust technique based on phase change, and in some cases, high temperature operation of the process equipment.

The following should be considered when designing a water purification system:

- the feed-water quality;
- the required water quality specification;
- the optimum generator size to avoid over-frequent start/stop cycling;
- blow-down and dump functions; and
- cool-down venting to avoid contamination ingress.

6. *Water purification, storage and distribution systems*

This section applies to WPU systems for PW, HPW and WFI. The water storage and distribution should work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment.

6.1 General

The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.



Once water has been purified using an appropriate method, it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following text describes the requirements for storage and distribution systems.

The storage and distribution system should be configured to prevent recontamination of the water after treatment and be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.

6.2 Materials that come into contact with systems for water for pharmaceutical use

This section applies to generation equipment for PW, HPW and WFI, and the associated storage and distribution systems.

The materials that come into contact with WPU, including pipe work, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.

- **Compatibility.** All materials used should be compatible with the temperature and chemicals used by or in the system.
- **Prevention of leaching.** All materials that come into contact with WPU should be non-leaching at the range of working temperatures.
- **Corrosion resistance.** PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipe work used. Appropriate sanitary-specification plastics and stainless steel materials are acceptable for WPU systems. When stainless steel is used it should be at least grade 316 L. The system should be passivated after initial installation or after modification. When accelerated passivation is undertaken, the system should be thoroughly cleaned first, and the passivation process should be undertaken in accordance with a clearly defined documented procedure.
- **Smooth internal finish.** Once water has been purified it is susceptible to microbiological contamination, and the system is subject to the formation of biofilms when cold storage and distribution is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre arithmetical mean roughness (Ra). When stainless steel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless steel material to surface corrosion.
- **Jointing.** The selected system materials should be able to be easily jointed by welding in a controlled manner. The control of the process should include as



a minimum, qualification of the operator, documentation of the welder set-up, work-session test pieces, logs of all welds and visual inspection of a defined proportions of welds.

- **Design of flanges or unions.** Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals are used and that they are fitted and tightened correctly.
- **Documentation.** All system components should be fully documented and be supported by original or certified copies of material certificates.
- **Materials.** Suitable materials that may be considered for sanitary elements of the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

6.3 System sanitization and bioburden control

Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitization or sterilizing the system after intervention for maintenance

or modification. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualification activities.

Systems that operate and are maintained at elevated temperatures, in the range of 70–80°C, are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed or the temperature requirements for the water in use, then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.5.3 for guidance).

6.4 Storage vessel requirements

The water storage vessel used in a system serves a number of important purposes. The design and size of the vessel should take into consideration the following.

6.4.1 Capacity

The capacity of the storage vessel should be determined on the basis of the following requirements.

- It is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points
- The water treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and equipment stress that occur when



the equipment cycles on and off too frequently.

- The capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session or other logical period of demand.

6.4.2 Contamination control considerations

The following should be taken into account for the efficient control of contamination.

- The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.
- Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.
- Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally be

configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered to prevent condensation within the filter matrix that might lead to filter blockage and to microbial growth through that could contaminate the storage vessels.

- Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.

6.5 Requirements for water distribution pipework

The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled.

Filtration should not usually be used in distribution loops or at takeoff user points to control biocontamination. Such filters are likely to conceal system contamination.

6.5.1 Temperature control and heat exchangers

Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or double plate and frame configuration should be considered. Where these types are not used,



an alternative approach whereby the utility is main- trained and monitored at a lower pressure than the WPU may be considered. Where heat exchangers are used they should be arranged in continually circulating loops or sub-loops of the system to avoid unacceptable static water in systems.

When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

6.5.2 Circulation pumps

Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

6.5.3 Biocontamination control techniques

The following control techniques may be used alone or more commonly in combination.

- Maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms. The main- tenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short- term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur.
- The system design should ensure the shortest possible length of pipework.
- For ambient temperature systems, pipework should be isolated from adjacent hot pipes.
- Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.
- Pressure gauges should be separated from the system by membranes.
- Hygienic pattern diaphragm valves should be used.
- Pipework should be laid to falls to allow drainage.
- The growth of microorganisms can be inhibited by:
 1. ultraviolet radiation sources in pipework;
 2. maintaining the system heated (guidance temperature 70–80°C);
 3. sanitizing the system periodically using hot water (guidance temperature >70°C);
 4. sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
 5. routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.



7. Operational considerations

7.1 Start-up and commissioning of water systems

Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

7.2 Qualification

WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

This guidance does not define the standard requirements for the conventional validation stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Phase 1: A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following should be included in the testing approach.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample the incoming feed-water daily to verify its quality.
- Sample after each step in the purification process daily.
- Sample at each point of use and at other defined sample points daily.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate production and delivery of product water of the required quality and quantity.
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
- Verify provisional alert and action levels.
- Develop and refine test-failure procedure.

Phase 2: A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase.



The approach should also:

- demonstrate consistent operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3: Phase 3 typically runs for 1 year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features.

- Demonstrate extended reliable performance.
- Ensure that seasonal variations are evaluated.
- The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

7.3 Continuous system monitoring

After completion of phase 3 of the qualification programme for the WPU system, a system review should be undertaken. Following this review, a routine monitoring plan should be established based on the results of phase 3.

Monitoring should include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use and specific sample points. Samples from points

of use should be taken in a similar way to that adopted when the water is being used in service.

Tests should be carried out to ensure that the selected pharmacopoeia specification has been satisfied, and should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, total viable count, presence of specific pathogens and endotoxins.

Monitoring data should be subject to trend analysis.

7.4 Maintenance of water systems

WPU systems should be maintained in accordance with a controlled, documented maintenance programme that takes into account the following:

- defined frequency for system elements;
- the calibration programme;
- SOPs for specific tasks;
- control of approved spares;
- issue of clear maintenance plan and instructions;
- review and approval of systems for use upon completion of work; and
- record and review of problems and faults during maintenance.

7.5 System reviews

WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance.



The review should consider matters such as:

- changes made since the last review;
- system performance;
- reliability;
- quality trends;
- failure events;
- investigations;
- out-of-specifications results from monitoring;
- changes to the installation;
- updated installation documentation;
- log books; and
- the status of the current SOP list.



ANNEX 6: HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide comfortable conditions for operators. These guidelines mainly focus on recommendations for systems for manufacturers of solid dosage forms. The guidelines also refer to other systems or components which are not relevant to solid dosage form manufacturing plants, but which may assist in providing a comparison between the requirements for solid dosage- form plants and other systems.

HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in Good manufacturing practices for pharmaceutical products (1) and should be

read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in the parent guide.

2. Scope of document

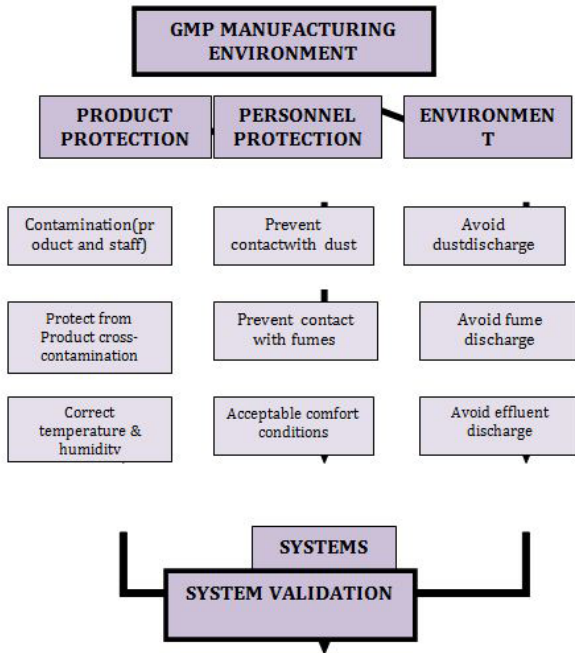
These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products.

These guidelines are intended as a basic guide for use by GMP inspectors. They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

Many manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next.



Figure 1: The guidelines address the various system criteria according to the sequence set out in this diagram



GMP, Good Manufacturing Practice

Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standard and ensuring that product quality and safety are not compromised. The three primary aspects addressed in this manual are the roles that the HVAC system plays in product protection, personnel protection and environmental protection (Fig. 1).



3. Glossary

The definitions given below apply to terms used in these guidelines. They may have different meanings in other contexts

Acceptance criteria

Measurable terms under which a test result will be considered acceptable.

Action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

Air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

Airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, personnel airlock; MAL, material airlock).

Alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

As-built

Condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

At-rest

Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

Central air-conditioning unit (see air-handling unit)

Change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

Clean area (clean room)

An area (or room) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.



Containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

Contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

Critical parameter or component

A processing parameter (such as temperature or humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

Cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

Design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

Design qualification (DQ)

DQ is the documented check of planning documents and technical specifications for conformity of the design with the process, manufacturing, GMP and regulatory requirements.

Direct impact system

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices.

Facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

Good engineering practice (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

Indirect impact system

This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only.

Infiltration

Infiltration is the ingress of contaminated air from an external zone into a clean area.

Installation qualification (IQ)

IQ is documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.



No-impact system

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to GEP only.

Non-critical parameter or component

A processing parameter or component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

Normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

Operating limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

Operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

Operating condition

This condition relates to carrying out room classification tests with the normal production process with equipment in operation, and the normal staff present in the room.

Operational qualification (OQ)

OQ is the documentary evidence to verify that the equipment operates in accordance with

its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

Oral solid dosage (OSD)

Usually refers to an OSD plant that manufactures medicinal products such as tablets, capsules and powders to be taken orally.

Performance qualification (PQ)

PQ is the documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

Point extraction

Air extraction to remove dust with the extraction point located as close as possible to the source of the dust.

Pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

Qualification

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.



Relative humidity

The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

Standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Turbulent flow

Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

Unidirectional airflow (UDAF)

Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

Validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Validation master plan (VMP)

VMP is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

4. Protection

4.1 Product and personnel

- 4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as "clean areas".
- 4.1.2 The achievement of a particular clean area classification depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area.
- 4.1.3 Some of the basic criteria to be considered should include:
 - building finishes and structure
 - air filtration
 - air change rate or flushing rate
 - room pressure

- location of air terminals and directional airflow
 - temperature
 - humidity
 - material flow
 - personnel flow
 - equipment movement
 - process being carried out
 - outside air conditions
 - occupancy
 - type of product.
- 4.1.4 Air filtration and air change rates should ensure that the defined clean area classification is attained.
- 4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required clean area classification.
- 4.1.6 Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:
- level of protection required
 - the quality and filtration of the supply air
 - particulates generated by the manufacturing process
 - particulates generated by the operators
 - configuration of the room and air supply and extract locations
 - sufficient air to achieve containment effect
 - sufficient air to cope with the room heat load
 - sufficient air to maintain the required room pressure.
- 4.1.7 In classifying the environment, the manufacturer should state whether this is achieved under “as-built” (Fig. 2), “at-rest” (Fig. 3) or “operational” (Fig. 4) conditions.

Figure 2. “As-built” condition

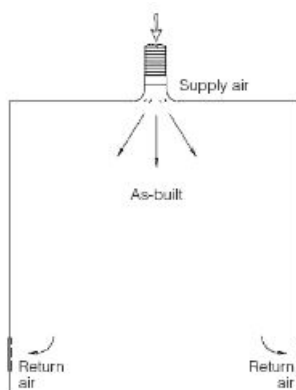




Figure 3. "At-rest" condition

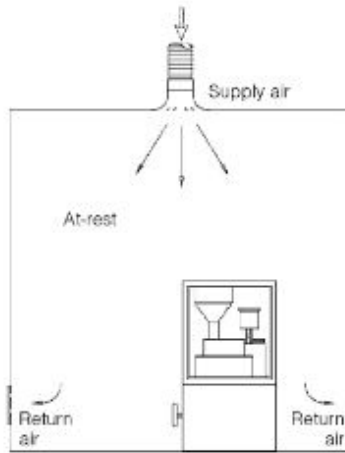
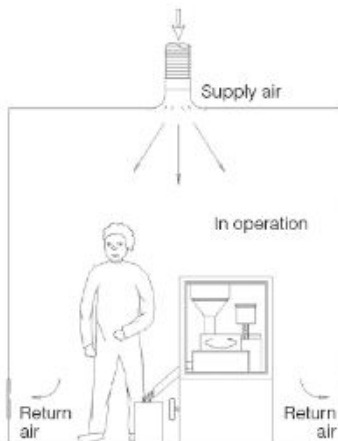


Figure 4. "Operational" condition

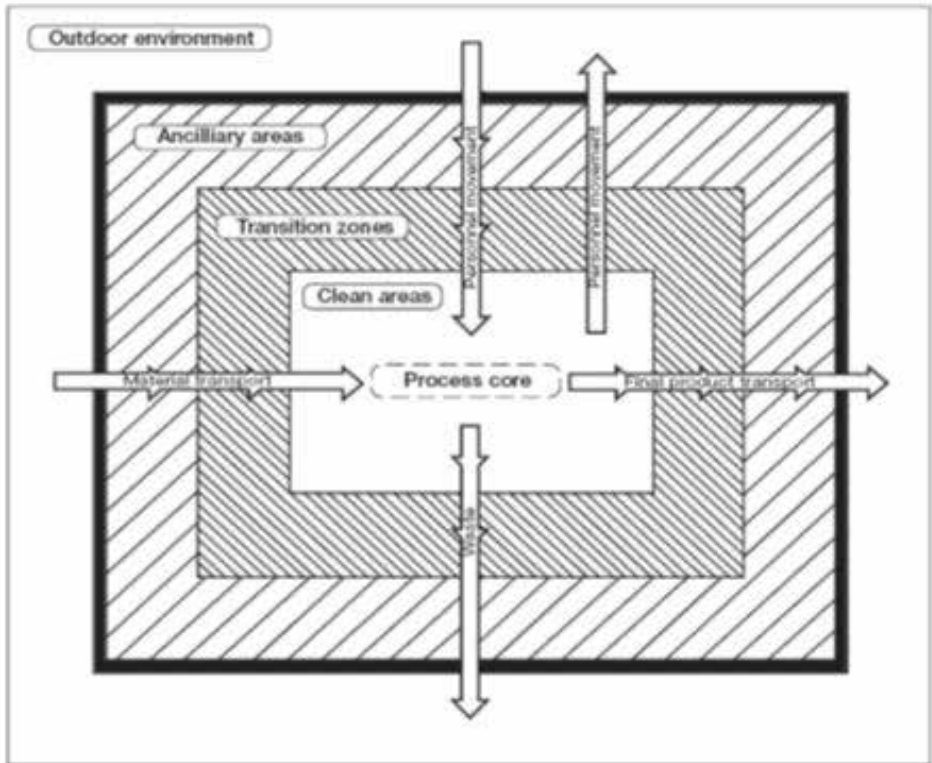




- 4.1.8 Room classification tests in the “as-built” condition should be carried out on the bare room, in the absence of any equipment or personnel.
- 4.1.9 Room classification tests in the “at-rest” condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility most clean area classifications are rated for the “at-rest” condition.
- 4.1.10 Room classification tests in the “operational” condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an “operational” condition should be able to be cleaned up to the “at-rest” clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.
- 4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 5.5 for cross-contamination control). Note: contaminants may result from inappropriate premises (e.g. poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, and a poor HVAC system.
- 4.1.12 Airborne contaminants should be controlled through effective ventilation.
- 4.1.13 External contaminants should be removed by effective filtration of the supply air. (See Fig. 5 for an example of a shell-like building layout to enhance containment and protection from external contaminants.)



Figure 5. Shell-like containment control concept



Note: The process core is regarded as the most stringently controlled clean zone which is protected by being surrounded by clean areas of a lower classification.

- 4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow. (See Figs 6 and 7 for examples of methods for the flushing of airborne contaminants.)
- 4.1.15 Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required.
- 4.1.16 The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product's susceptibility to degradation (Table 1).

4.2 Air filtration

Note: The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination.

- 4.2.1 The type of filters required for different applications depend on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 2 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

Figure 6. Turbulent dilution of dirty air

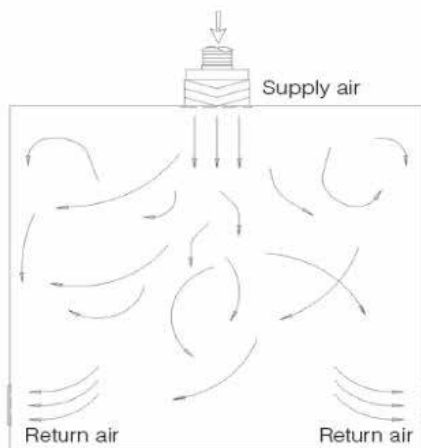




Figure 7. Unidirectional displacement of dirty air

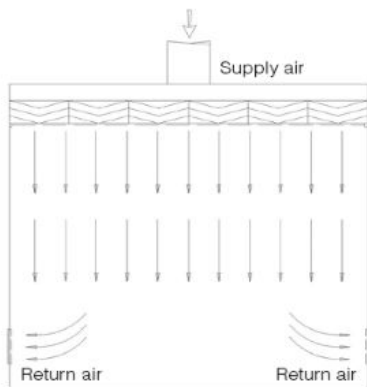


Table 1. Examples of levels of protection

Level	Condition	Example of area
Level 1	General Area	with normal housekeeping and maintenance, e.g. ware- housing, secondary packing
Level 2	Protected Area	in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing
Level 3	Controlled Area	in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product

**Table 2. Levels of protection and recommended filtration**

Level of Protection	Example of area
Level 1	Primary filters only (e.g. EN779 G4 filters)
Level 2 and 3	Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters)
Level 2 and 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN779 G4 plus F8 plus EN1822 H13 filters)

Note: The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

- 4.2.2 Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods each result in a different value for the same filter) (Fig. 8).
- 4.2.3 In selecting filters, the manufacturer should have considered other factors, such as particularly contaminated ambient conditions, local regulations and specific product requirements. Good pre-filtration extends the life of the more expensive filters downstream.
- 4.2.4 Materials for components of an HVAC system should be selected with care so that they do not become the source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.
- 4.2.5 Ventilation dampers, filters and other services should be designed and positioned so that they are accessible from outside the manufacturing areas (service voids or service corridors) for maintenance purposes.



Figure 8. Comparison of filter test standards

EU Class	Percentage (Integral value)		EN779 EN 1822
	99.99995		U16
	99.9995		U15
14	99.995		H14
13	99.95		H13
12			
11	Percentage (average) 99.5		H12
10	95		H11
9	95	85	F9/H10
8	90	75	F8
	85		F7
7	80		
	75		
6	70		F6
	65		
	60		
	55		
5	50		F5
	45		
	Percentage (average) 40		
	35		
4	95	30	G4
	90	25	
3	85	20	G3
	80		
	75		
2	70		G2
	65		
			G1

Eurovent Class -
Eurovent 49 (2-9)
Eurovent 49 (2-9)
Eurovent 44 (10-14)

Arrestance (%)

Dust spot efficiency
ASHRAE 52/76
B56540 Part 1 (1995)

MPPS, DEHS Aerosol
EN1822

GEN/TC195
WG1-G1-F9
WG2-H10-16

EN?1822?

↑

EN?779?

↓

EN, European norm (Euronorm); EU, European Union.

This figure gives a rough comparison between the different filter standards (filter classes should always be connected to the standard test method).

- 4.2.6 Personnel should not be a source of contamination.
- 4.2.7 Directional airflow within production or packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.
- 4.2.8 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.
- 4.2.9 Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. (See Figs 9–11 for illustrations of the three types of diffuser.)
- 4.2.10 Whenever possible, air should be exhausted from a low level in rooms to help provide a flushing effect.
- 4.3 Unidirectional airflow**
- 4.3.1 Unidirectional airflow (UDAF) should be used where appropriate to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas.

Figure 9. Induction diffuser (not recommended)

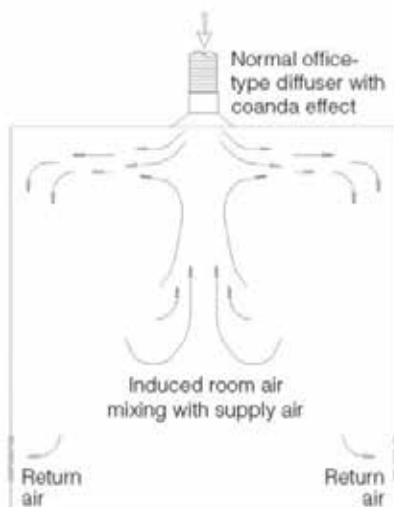




Figure 10. Perforated plate diffuser (recommended)

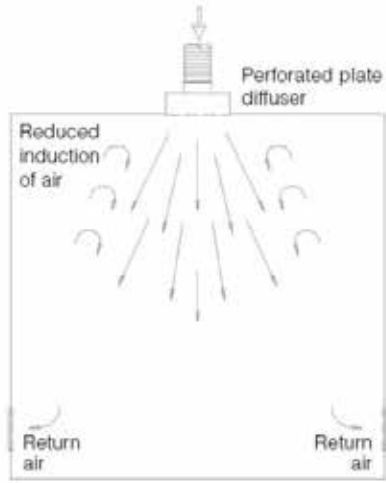
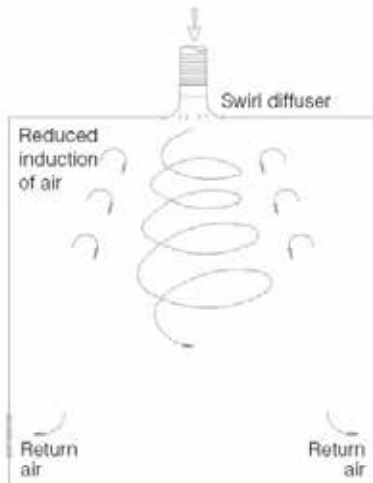


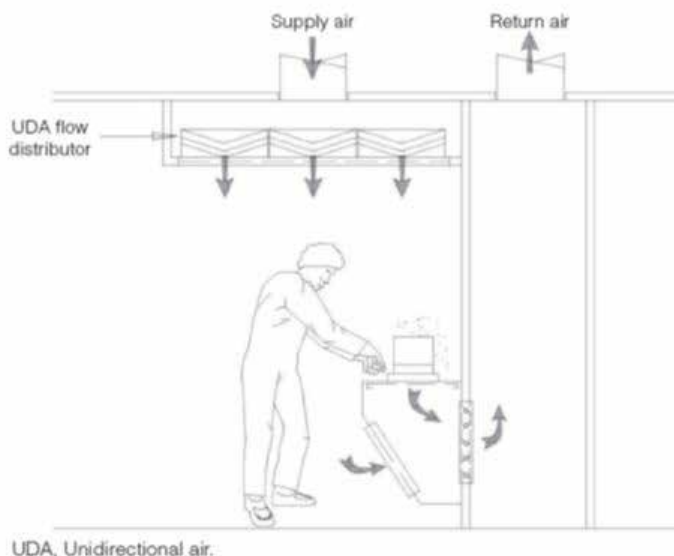
Figure 10. Perforated plate diffuser (recommended)



- 4.3.2 Where appropriate, the unidirectional airflow should also provide protection to the operator from contamination by the product.
- 4.3.3 Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for the further processing of the product.
- 4.3.4 In a weighing booth situation, the aim of the design using UDAF should be to provide dust containment.
- 4.3.5 A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator.
- 4.3.6 The source of the dust and the position in which the operator normally stands should be determined before deciding on the direction of unidirectional flow.

Example: In Fig. 12 the dust generated at the weighing station is immediately extracted through the perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

Figure 12. Operator protection at weighing station





- 4.3.7 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment.
- 4.3.8 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Fig. 13).
- 4.3.9 Once the system has been designed and qualified with a specific layout for operators and processes, this should be maintained in accordance with an SOP.
- 4.3.10 There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

Fig. 14 illustrates the incorrect use of a weighing scale which has a solid back. The back of the weighing scale should not block the return air path as this causes air to rise vertically, resulting in a hazardous situation for the operator.

Fig. 15 illustrates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this would carry dust up towards the operator's face.

Fig. 16 shows that a solid worktop can sometimes cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible solution would be to have a 100 mm gap between the back of the table and the wall, with the air being extracted here.

- 4.3.11 The manufacturer should select either vertical or horizontal unidirectional flow (Fig. 17) and an appropriate airflow pattern to provide the best protection for the particular application.

4.4 Infiltration

- 4.4.1 Air infiltration of unfiltered air into a pharmaceutical plant should not be the source of contamination.
- 4.4.2 Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure to prevent the escape of harmful products to the outside (such as penicillin and hormones), special precautions should be taken.
- 4.4.3 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

Figure 13. Operator protection by horizontal airflow

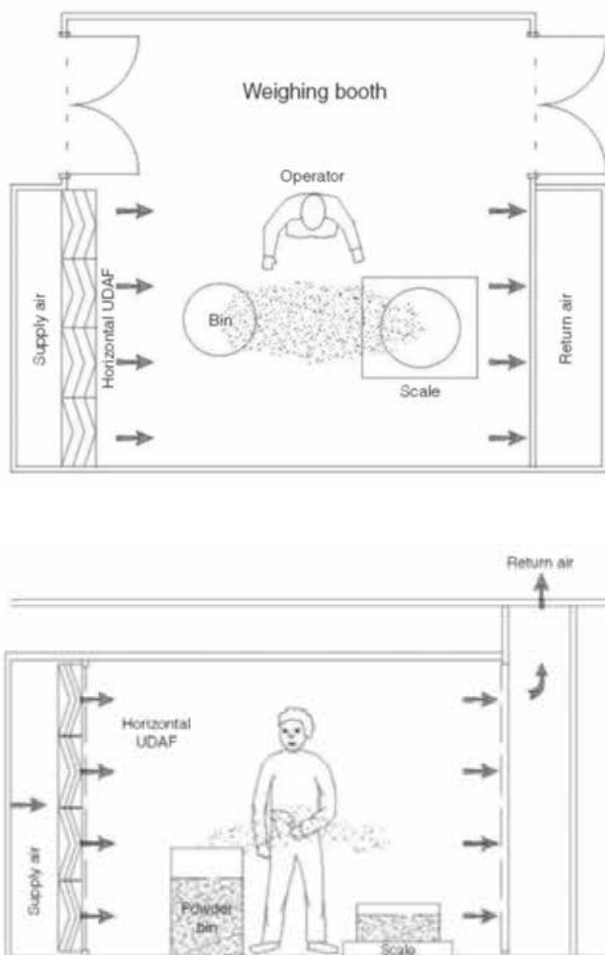




Figure 14. Operator subject to powder inhalation due to obstruction

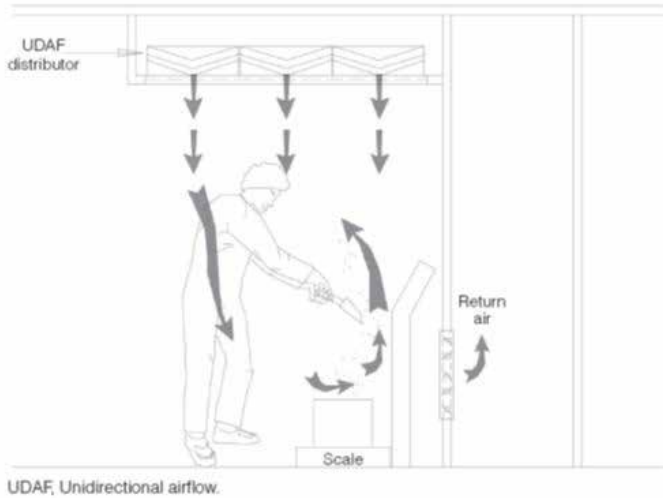


Figure 15. Operator subject to powder contamination due to airflow reversal in bin

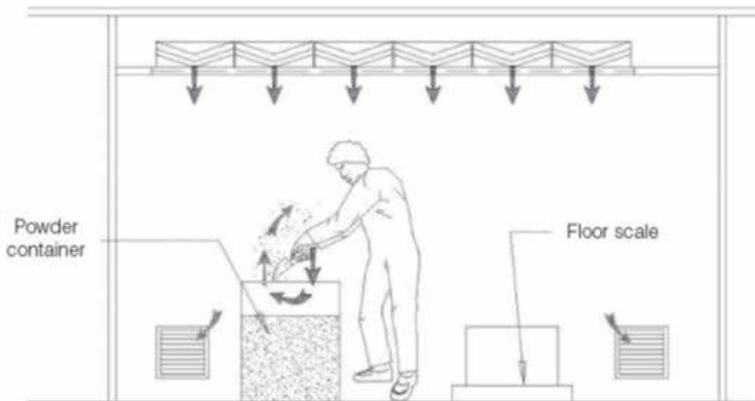


Figure 16. Operator subject to powder inhalation due to worktop obstruction

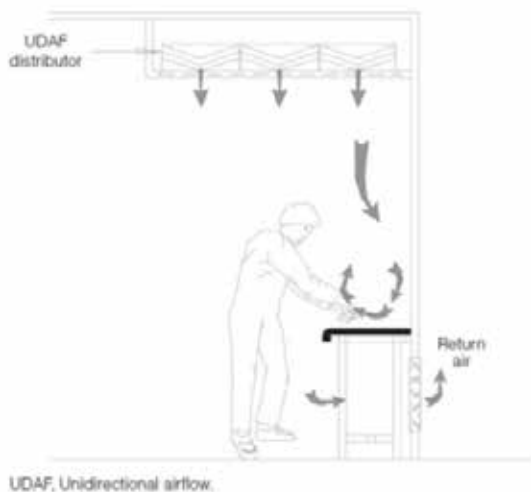
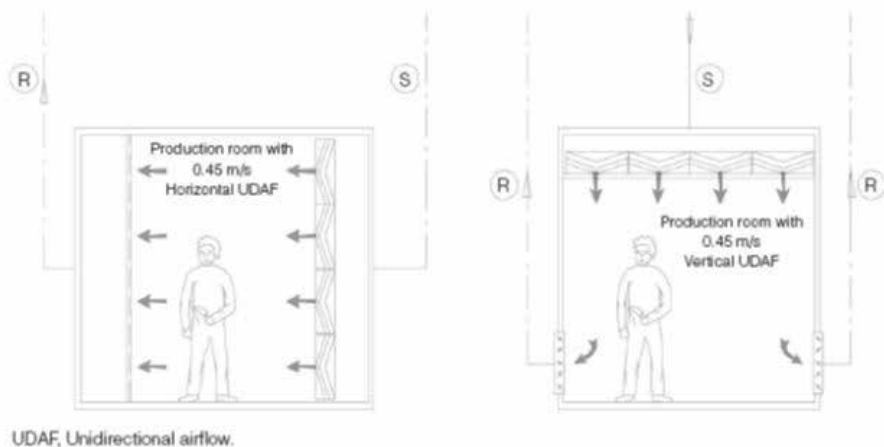


Figure 17. Diagram indicating horizontal and vertical unidirectional flow





4.4.4 Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

4.5 Cross-contamination

4.5.1 Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.

4.5.2 Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

4.5.3 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

4.5.4 Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

4.5.5 The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.

4.5.6 Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

4.5.7 The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.

4.5.8 Building structure should be given special attention to accommodate the pressure cascade design.

4.5.9 Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.

Displacement concept (low pressure differential, high airflow)

Note: This method of containment is not the preferred method, as the measurement and monitoring of airflow velocities in doorways is difficult. This concept should ideally be applied in production processes where large amounts of dust are generated.

4.5.10 Under this concept the air should be supplied to the corridor, flow through the doorway, and be extracted from the back of the cubicle. Normally the cubicle door should be closed and the air should enter the cubicle through a door grille, although the concept can be applied to an opening without a door.

4.5.11 The velocity should be high enough to prevent turbulence within the doorway resulting in dust escaping.



4.5.12 This displacement airflow should be calculated as the product of the door area and the velocity, which generally results in fairly large air quantities.

Pressure differential concept (high pressure differential, low airflow)

Note: The pressure differential concept may normally be used in zones where little or no dust is being generated. It may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

4.5.13 The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle.

4.5.14 The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

4.5.15 In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration.

Note: The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of 3 Pa is specified, the implications of the upper and lower tolerances on containment should be evaluated.

4.5.16 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tolerance and the second room is at the minimum tolerance.

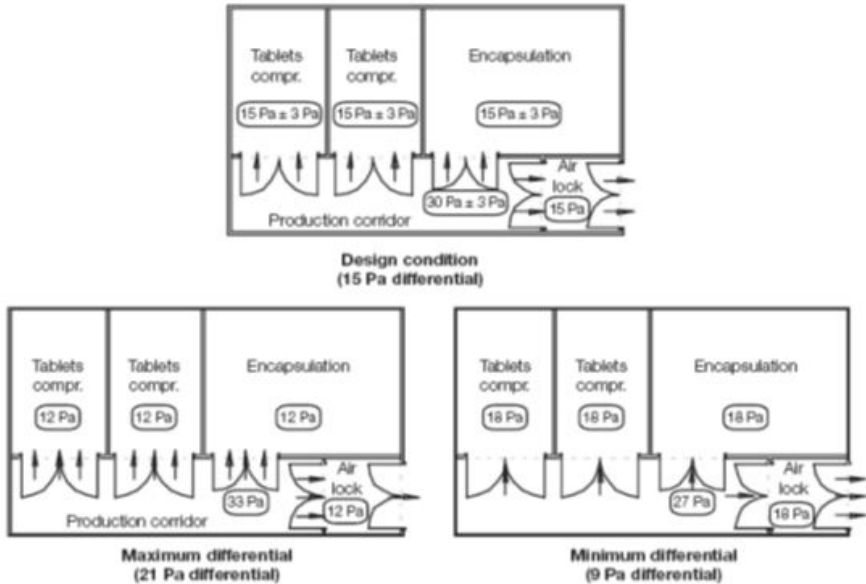
4.5.17 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

4.5.18 The effect of room pressure tolerances are illustrated in Fig. 18.

4.5.19 The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis.



Figure 18. Examples of pressure cascades



- 4.5.20 Manual control systems, where used, should be set up during commissioning and should not change unless other system conditions change.
- 4.5.21 Airlocks can be important components in setting up and maintaining pressure cascade systems.
- 4.5.22 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figs 19–21).
- Cascade airlock: high pressure on one side of the airlock and low pressure on the other.
 - Sink airlock: low pressure inside the airlock and high pressure on both outer sides.
 - Bubble airlock: high pressure inside the airlock and low pressure on both outer sides.
- 4.5.23 Doors should open to the high pressure side, and be provided with self-closers. Door closer springs, if used, should be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors are not recommended.
- 4.5.24 Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.

Figure 19. Example of cascade airlock

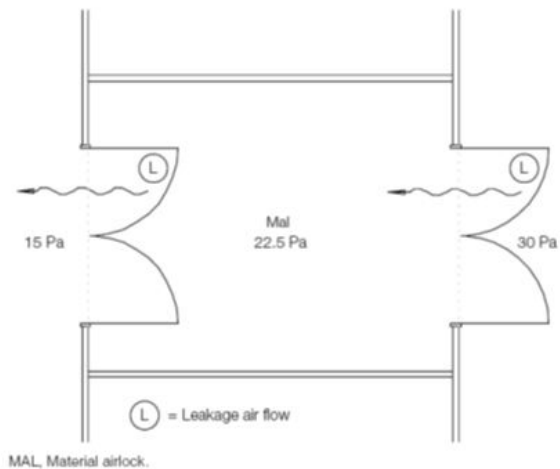


Figure 20. Example of sink airlock

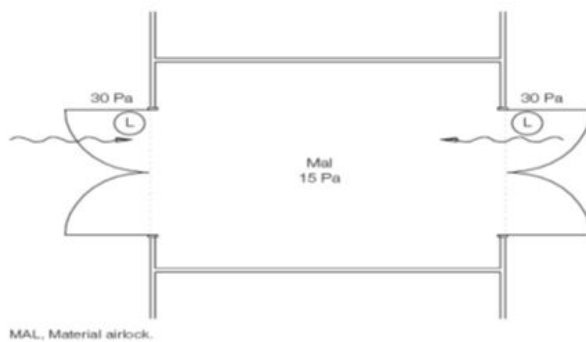
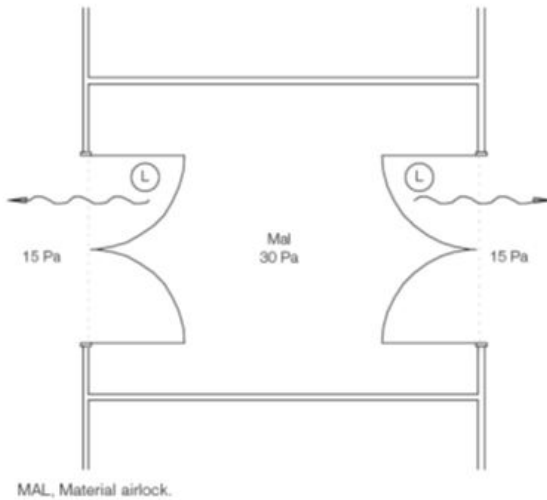




Figure 21. Example of bubble airlock



- 4.5.25 Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.
- 4.5.26 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

Physical barrier concept

- 4.5.27 Where appropriate, an impervious barrier to prevent cross-contamination between two zones, such as barrier isolators or pumped transfer of materials, should be used.

- 4.5.28 Spot ventilation or capture hoods may be used as appropriate.

4.6 Temperature and relative humidity

- 4.6.1 Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products, and to provide a comfortable environment for the operator where necessary.
- 4.6.2 Maximum and minimum room temperatures and relative humidity should be appropriate.
- 4.6.3 Temperature conditions should be



- adjusted to suit the needs of the operators while wearing their protective clothing.
- 4.6.4 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.
- 4.6.5 Cubicles, or suites, in which products requiring low humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher humidity by means of suitable airlocks.
- 4.6.6 Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.
- 4.6.7 Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.
- 4.6.8 Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.
- 4.6.9 Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.
- 4.6.10 Humidifiers should be avoided if possible as they may become a source of contamination (e.g. Microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.
- 4.6.11 Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system.
- 4.6.12 Humidification systems should be well drained. No condensate should accumulate in air-handling systems.
- 4.6.13 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.
- 4.6.14 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.
- 4.6.15 Air filters should not be installed immediately downstream of humidifiers.
- 4.6.16 Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.
- 4.6.17 When specifying relative humidity, the associated temperature should also be specified.



- 4.6.18 Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.
- 5. Dust control**
- 5.1 Wherever possible, the dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed.
- 5.2 Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood.
- 5.3 or a fixed extraction hood. Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting.
- 5.4 The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).
- 5.5 Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product.

Figure 22. Protective garments





- 5.6 Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.
- 5.7 Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room.
- 5.8 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room.
- 5.9 The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.
- 5.10 When planning the system for the extraction of vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.
- 5.11 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.
- 5.12 When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments, as indicated in Fig. 22. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.
- 5.13 The rates at which fresh air is supplied to the facility should comply with national, regional and/or international regulations, to provide operators with an acceptable level of comfort and safety and also to remove odours or fumes.
- 5.14 The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.
- 6. Protection of the environment**
- 6.1 Dust in exhaust air**
- 6.1.1 Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.



- 6.1.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN779 filter standards.
- 6.1.3 Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.
- 6.1.4 For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection should the first filter fail.
- 6.1.5 When handling hazardous compounds, safe-change filter housings, also called "bag-in-bag-out" filters, should be used.
- 6.1.6 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading.
- 6.1.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.
- 6.1.8 Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.
- 6.1.9 Sophisticated computer-based data monitoring systems may be installed, with which preventive maintenance is planned by trend logging (This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system.)
- 6.1.10 An automated monitoring system should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system.
- 6.1.11 Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.
- 6.1.12 Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross-contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.
- 6.1.13 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.



- 6.1.14 When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.
- 6.1.15 The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.
- 6.1.16 Where necessary, additional filtration may be provided downstream of the dust collector.

6.2 Fume removal

- 6.2.1 The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross- contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.
- 6.2.2 Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).
- 6.2.3 Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.
- 6.2.4 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

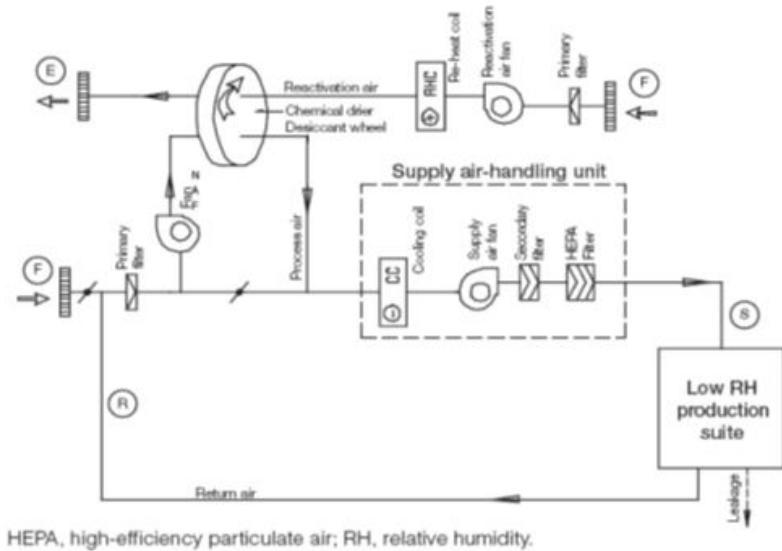
- 6.2.5 The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

7. HVAC systems and components

Note: The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters provided the air is not re-circulated. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8, "at-rest" condition, measured against particle sizes of 0.5 μ m and 5 μ m, but cleanliness may not be classified as such by manufacturers.



Figure 23. Air-handling system with chemical drying



7.1 General

7.1.1 There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.2 A schematic diagram of the airflow for a typical system serving a low humidity suite is represented in Fig. 23.

7.1.3 Air should be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated

by means of passing hot air through one segment of the wheel).

7.1.4 The figure illustrates the chemical drier handling part of the fresh air/ return air mixture on a by-pass flow. The location of the chemical drier should be considered in the design phase. Examples of appropriate locations include:

- full flow of fresh/return air;
- partial handling of fresh/return air (by-pass airflow);
- return air only;
- fresh air only; or
- pre-cooled air with any of the above alternatives.



- 7.1.5 Possible additional components that may be required should be considered depending on the climatic conditions and locations. These may include items such as:
- frost coils on fresh air inlets in very cold climates to preheat the air;
 - snow eliminators to prevent snow entering air inlets and blocking airflow;
 - dust eliminators on air inlets in arid and dusty locations;
 - moisture eliminators in humid areas with high rainfall; and
 - fresh air pre-cooling coils for very hot or humid climates.
- 7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails.
- 7.1.7 Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area classification, e.g. where ceiling return air grilles are used.
- 7.1.8 There may be alternative locations for return air. For example, referring to Fig. 24, room D (low-level return air) and room E (ceiling return air).

The airflow schematics of the two systems (Figs 24 and 25) indicate air-handling unit with return air or re-circulated air, having a percentage of fresh air added. Fig. 25 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms A, B and C, respectively.

The airflow diagram in Fig. 24 is an example of a typical system with a lower clean area classification.

Note: There are two basic concepts of air delivery to pharmaceutical production facilities: a recirculation system, and a full fresh air system (100% outside air supply).

7.2 Recirculation system

- 7.2.1 There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.
- 7.2.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.



Figure 24. Air-handling system with high-efficiency particulate air filters in air-handling unit

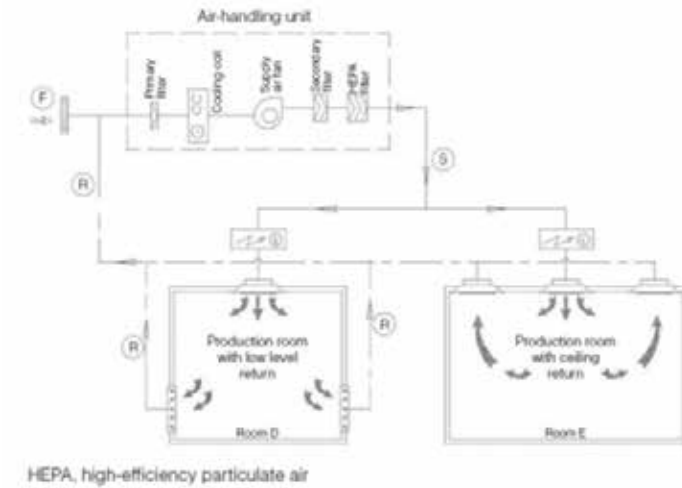


Figure 25. Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow

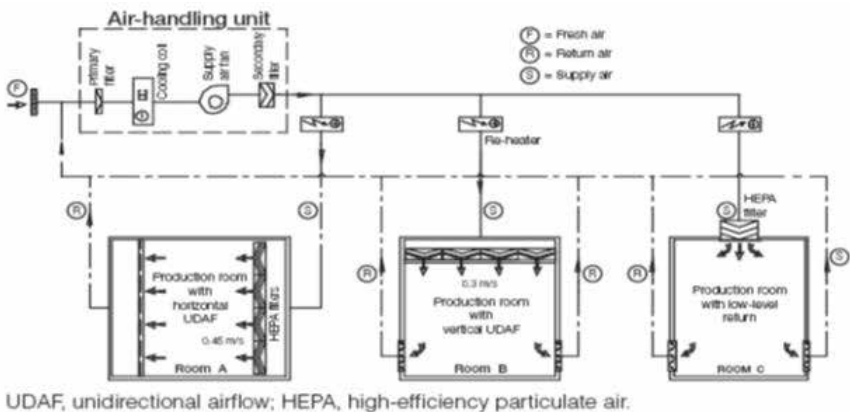
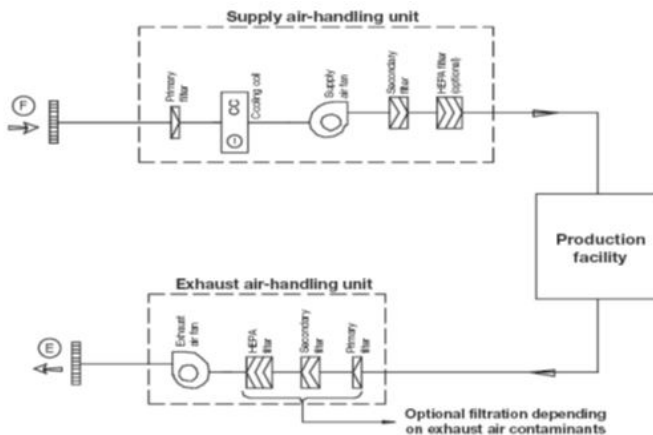


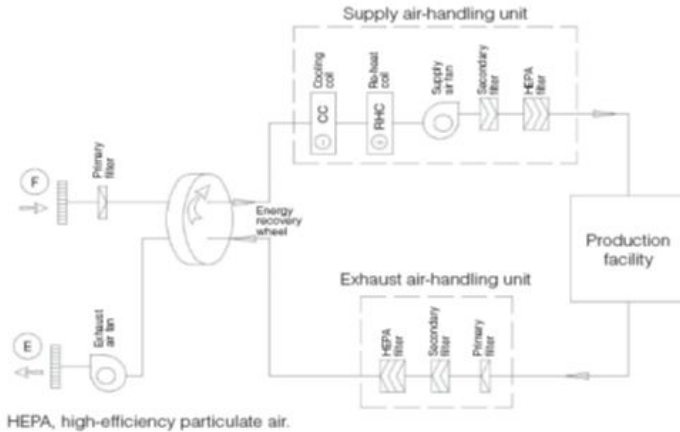
Figure 26. Full fresh-air system



- 7.2.3 HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.
 - 7.2.4 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.
 - 7.2.5 HEPA filters may be located in the air-handling unit or placed terminally.
 - 7.2.6 Air containing dust from highly toxic processes should never be recirculated to the HVAC system.
 - 7.2.7 Full fresh-air systems
Fig. 26 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided.
 - 7.2.8 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations.
 - 7.2.9 Energy-recovery wheels should normally not be used in multiproduct facilities. When such wheels are used they should not become a source of possible contamination (see Fig. 27).
- Note:** Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.



Figure 27. Full fresh-air system with energy recovery



7.2.10 The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

in the user requirement specification (URS), and capacities as specified by the designer or developer.

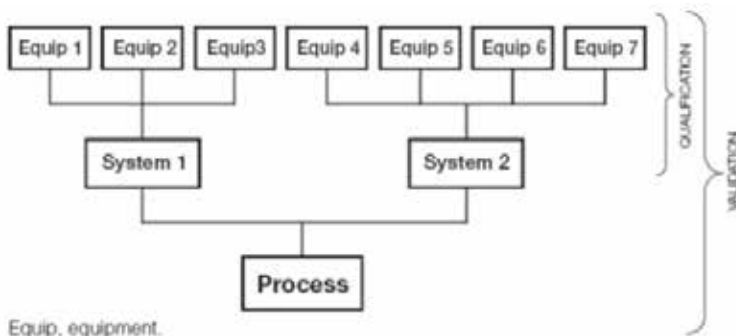
8.1.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

7. Commissioning, qualification and maintenance

8.1 Commissioning

8.1.1 Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified

Figure 28. Qualification is a part of validation



Equip, equipment.

- | | |
|--|--|
| <p>8.1.3 The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).</p> <p>8.1.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.</p> <p>8.1.5 Training should be provided to personnel after installation of the system, and should include operation and maintenance.</p> <p>8.1.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.</p> | <p>8.1.7 Commissioning should be a precursor to system qualification and process validation.</p> <p>8.2 Qualification</p> <p>8.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of these guidelines. Qualification and validation guidelines are included in: Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 937), Annex 4 (see also Fig. 28).</p> <p>Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out below.</p> <p>8.2.2 The qualification of the HVAC system should be described in a validation master plan (VMP).</p> |
|--|--|



- 8.2.3 It should define the nature and extent of testing and the test procedures and protocols to be followed.
- 8.2.4 Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.
- 8.2.5 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.
- 8.2.6 Any parameter that may affect the quality of the pharmaceutical product, or a direct impact component, should be considered a critical parameter.
- 8.2.7 All critical parameters should be included in the qualification process.
- Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.
- Example:**
- The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity controlled air, is further removed from the product and may not require operational qualification.
 - A room cleanliness classification is a critical parameter and, therefore, the room air change rates and HEPA filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.
- 8.2.8 Non-critical systems and components should be subject to GEP and may not necessarily require qualification.
- 8.2.9 A change control procedure should be followed when changes are planned to the direct impact HVAC system, its components and controls that may affect critical parameters.
- 8.2.10 Acceptance criteria and limits should be defined during the design stage.
- 8.2.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.
- 8.2.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.
- 8.2.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

8.2.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

8.2.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Fig. 29.

8.2.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

Figure 29. System operating ranges



8.2.17 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

- temperature
- relative humidity
- supply air quantities for all diffusers
- return air or exhaust air quantities
- room air change rates
- room pressures (pressure differentials)
- room airflow patterns
- unidirectional flow velocities
- containment system velocities
- HEPA filter penetration tests
- room particle counts
- room clean-up rates
- microbiological air and surface counts where appropriate
- operation of de-dusting warning/alarm systems where applicable.

**Table 3. Part A: schedule of tests to demonstrate compliance (for reference purposes only)**

Schedule of tests to demonstrate continuing compliance

Test parameter	Clean room class	Max. time interval	Test procedure
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5*
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13*
Airflow velocity (To verify laminar flow or containment conditions)	All Classes	12 Months	Air velocities for containment systems and laminar flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4*



8.2.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.

Note: Table 3 gives intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process.

8.2.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

8.2.20 Requalification should also be done when any change, which could affect system performance, takes place.

8.2.21 Clean-up or recovery times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest" and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at rest" condition.

**Table 3. Part B: recommended optional strategic tests (ISO 14644)**

Schedule of tests to demonstrate continuing compliance

Test parameter	Clean room class	Max. time interval	Test procedure
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	Demonstrate that contaminant is maintained within a room by means of: <ul style="list-style-type: none">• airflow direction smoke tests• room air pressures. In accordance with ISO 14644-3 Annex B4*
Recovery (To verify clean- up time)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All Classes	24 Months	Tests to demonstrate airflows: <ul style="list-style-type: none">• from clean to dirty areas• do not cause cross-contamination• uniformly from laminar flow units. Demonstrated by actual or video- taped smoke tests. In accordance with ISO 14644-3 Annex B7*



8.3 Maintenance

8.3.1 There should be a planned preventive maintenance program, procedures and records for the HVAC system. Records should be kept.

8.3.2 Maintenance personnel should receive appropriate training.

8.3.3 HEPA filters should be changed either by a specialist or a trained person.

8.3.4 Any maintenance activity should be assessed critically to determine any impact on product quality including possible contamination.

8.3.5 Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for requalification of an area as a result of an interruption of the service.



ANNEX 7: AUTHORIZED PERSONS

7.1 The authorized person is defined as a person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale.

The role and position of the authorized person in the company

7.2 The authorized person as the overall quality controller will be a member of a team whose function includes the following major areas:

- implementation (and, when needed, establishment) of the quality system;
- participation in the development of the company's quality manual;
- supervision of the regular internal audits or self-inspections;
- oversight of the quality control department;
- participation in external audit (vendor audit);
- participation in validation programs.

7.3 Although authorized persons may not have line management responsibility for many activities within this function (although they should be involved in these activities as much as possible), they must be aware of any changes that may affect compliance with technical or regulatory requirements related to the quality of finished products. When any aspect of the company's operations is not in accordance with GMP guidelines or relevant legislation in force, the authorized person must bring this to the attention of senior management. This duty should be reflected in the authorized person's job description.

7.4 The availability of an authorized person should be a prerequisite for issue of a manufacturing license (authorization). The authorized person (as well as persons responsible for production and quality control) must be approved by the NMRA. The marketing authorization holder is obliged to inform the NMRA, or other responsible authority depending on national (regional) regulations, immediately if the authorized person is replaced unexpectedly. Such provisions will assure to a considerable degree the independence of the authorized person from the management of the company in the fulfillment of his or her duties even when under pressure to depart from professional and technical standards.

7.5 More than one authorized persons may be designated A company may have a complex structure, or operate at several locations, or both, and sometimes a separate authorized person may be designated who is responsible for the manufacture of clinical trial materials. Consequently it may be necessary to nominate several authorized persons, one of them having the responsibilities of the overall quality controller and the others responsible for site or branch operations or specific products. The person authorizing batch release should be independent from production and quality control activities.



- 7.6 The drug regulatory authority should approve the authorized person on the basis of his or her professional curriculum vitae. Authorized persons have duties not only to their employer but also to the competent authorities such as the drug regulatory authority. They should establish good working relations with inspectors and as far as possible provide information on request during site inspections.
- 7.7 The authorized person depends upon many working colleagues for the achievement of quality objectives, and may delegate some duties to appropriately trained staff while remaining the overall quality controller. It is therefore of paramount importance that he or she establish and maintain a good working relationship with other persons in positions of responsibility, especially those responsible for production and quality control.
- 7.8 The authorized person must ensure that there is a quality manual describing the quality policy and objectives (commitment to quality) of the company, the organizational structure, responsibilities and authorities, together with a description of or references to documented quality system procedures.
- 7.9 The Authorized person must ensure that Research and development activities and the transfer of results of the developmental work to routine manufacture, including original product design, formulation, processes development and validation, should observe GMP principles as guidance. Batches produced for clinical trials must follow applicable GMP. It is of vital importance that the quality of routine production batches corresponds to a specification derived from the composition of development batches. The quality and safety of a pharmaceutical product depend on the application of appropriate procedures, based on GMP, leading to a product within the recognized specification. Standard procedures and recognized specifications cannot be separated.
- 7.10 The Authorized person must ensure that each batch of finished products has been manufactured in accordance with the marketing authorization, GMP rules and all related legal and administrative provisions. This does not necessarily mean that they must have directly supervised all manufacturing and quality control operations. They must be satisfied either directly or, more usually, by proper operation of quality systems that manufacturing and testing have complied with

Implementation of the quality system

- 7.8 Authorized persons have a personal and professional responsibility for ensuring that each batch of finished products has been manufactured in accordance with the marketing authorization, GMP rules and all related legal and administrative provisions. This does not necessarily mean that they must have directly supervised all manufacturing and quality control operations. They must be satisfied either directly or, more usually, by proper operation of quality systems that manufacturing and testing have complied with



Routine duties of an authorized person

7.11 Before approving a batch for release the authorized person doing so should always ensure that the following requirements have been met:

- The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.
- The principles and guidelines of GMP have been followed.
- The principal manufacturing and testing processes have been validated, if different.
- All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records.
- Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to and approval by the drug regulatory authority.
- Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations.
- All necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
- Appropriate audits, self-inspections and spot-checks are being carried out by experienced and trained staff.
- Approval has been given by the head of the quality control department.

- All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g., subdivision of output batches from a common input, factors associated with continuous production runs).

7.12 In certain circumstances the authorized person may be responsible for the release of intermediates manufactured on contract.

Education and training

7.13 The basic qualifications of a scientific education and practical experience for key personnel, including authorized persons, are outlined in chapter 2 (Personnel).

Professional Experience

7.14 Depending on the type of activity and professional knowledge, the required experience shall range from a minimum of 1 year up to 4 years.

The experience expected includes primarily the following points:

- 7.14.1 technical know-how of the processes an authorized person will be responsible for,
- 7.14.2 for manufacturing, import and wholesale including market release of pharmaceutical products: knowledge and experience of GMP,



- 7.14.3 for the import, wholesale, export and trade in foreign countries: knowledge and experience of GDP,
- 7.14.4 for manufacturing, import and wholesale of blood and blood products including market release of labile blood products: knowledge and experience of blood collection for transfusion, haematology or blood transfusion.
- International Standards ISO 9000 - 9004 and relationships with suppliers, principles and problems of formulation of pharmaceutical preparations, pharmaceutical microbiology, and principles and practice of sampling and testing of starting materials, packaging components and finished dosage forms.

This experience can be acquired:

- by activities where the individual is in charge of, or partially responsible for, the manufacturing of medicinal products or transplant products (GMP), or the wholesale of medicinal products (GDP),
 - by involvement in quality assurance work within a company that manufactures medicinal products or transplant products,
 - or possibly by means of experience with regulatory issues, such as the drafting of the quality modules of the CTDs /eCTDs within the framework of authorization procedures,
 - by executing advisory or inspectory activities in the respective field.
- 7.15 Additional requirements may include subjects such as principles of quality assurance and GMP, principles of good laboratory practice as applicable to research and development as well as to quality control, detailed knowledge of the authorized/qualified person's duties and responsibilities, of



ANNEX 8: QUALITY RISK MANAGEMENT (QRM)

1. INTRODUCTION

1.1 Background and scope

In most countries compliance with good manufacturing practices (GMP) (1, 2) (including validation), drug regulatory activities and inspections, together with supply chain controls throughout the product life-cycle, provide good assurance that risks are largely controlled. However, where control is less effective, patients may be put at risk through the production of medicines of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources. Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it via appropriate and robust controls.

The aim of this guideline is to assist the development and implementation of effective QRM covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. In the past, hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management guidance to the pharmaceutical industry (3). Since then international guidance has emerged (2, 4-8) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently,

this WHO guideline has been developed as an update of WHO advice to the pharmaceutical industry, taking account of this new guidance.

In order to protect patients, in terms of quality, safety and efficacy, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product. Some MRAs are requiring the adoption of a risk-based approach for certain specific areas in the life-cycle of a pharmaceutical product, e.g. for environmental monitoring for sterile products manufacturing.

While the choice of the tools to support the QRM approach is optional and may vary, they need to be appropriate for the intended use. In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers(9)as summarized in the following sections.

- a) Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers:
 - **MRAs:** systematic and structured planning of reviews and inspections that are risk-based. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - **Manufacturers:** design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system (PQS).



- b) Science-based decision-making can be embedded into QRM processes:
- **MRAs:** decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.
 - **Manufacturers:** quality decisions and filing commitments can be based on science-based process understanding and QRM (when utilizing the quality by design approach). Its effective application should offer manufacturers greater freedom on how to meet principles of GMP, and this, therefore, should encourage innovation.
- The control strategy for the process focuses on critical quality attributes and critical process parameters. Uncertainty can be addressed explicitly.
- c) Resources can be focused on risks to patients:
- **MRAs:** QRM can be used to determine best allocation of inspection resource, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.
- **Manufacturers:** evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient by ensuring the quality, safety and efficacy of the product. A corporate culture is supported to produce cost-effective medicines, without compromising quality, while maintaining focus on the patient as a primary stakeholder in all activities.
- d) Restrictive and unnecessary practices can be avoided:
- **MRAs:** regulatory scrutiny adjusted to level of risk to patients. Improvement and innovation by manufacturers should be encouraged.
 - **Manufacturers:** instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Innovation and the adoption of the latest scientific advances in manufacturing and technology are supported.
- Unnecessary testing can be eliminated, for example, with real-time release testing.**
- e) Communication and transparency are facilitated:
- **MRAs:** facilitate dialogue with pharmaceutical manufacturers and clarify to the industry and the public on how the inspection programme may be adjusted based on the risk to patients. Information-



sharing between MRAs will contribute to a better risk management approach globally.

- **Manufacturers:** matrix team approach, stakeholders kept informed via science-based decisions. Culture of trust and “one-team” mindset with focus on product and patient.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout its life-cycle in order to optimize its benefit/risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

This guideline will align with the general framework described within other current international guidance on this subject.

1.2 Principles of quality risk management

The two primary principles of QRM are:

- evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient; and
- the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

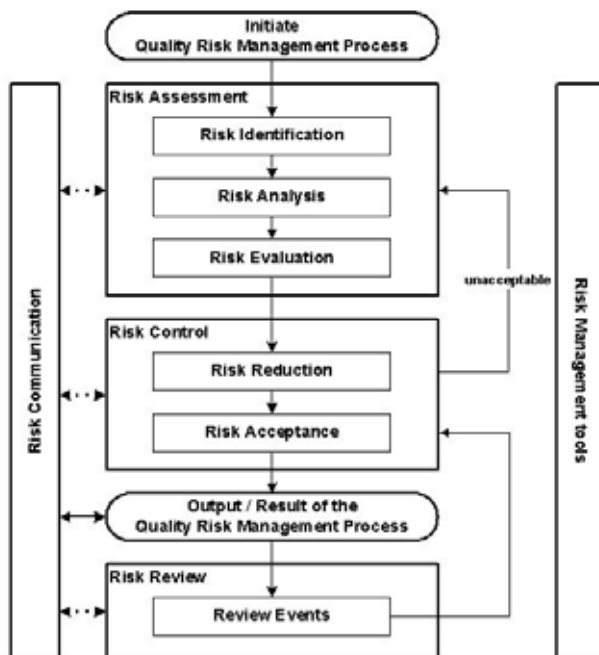
Beside these the following principles are also part of the QRM methodology:

- when applied, processes using QRM methodologies should be dynamic, iterative and responsive to change; and

- the capability for continual improvement should be embedded in the QRM process.

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 and illustrated in Figure 1 (reproduced from ICH Q9). The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1. Overview of a typical quality risk management process



Taken from reference 6: ICH Q9: Quality Risk Management. This figure is also available on the ICH website www.ich.org

Decision points are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision.

Note: “unacceptable” in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also indicates that the risk assessment process should be revisited.

The approach described in this guideline should be used to:

- systematically analyze products and processes to ensure the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;



- provide a communication process that will best interface with all relevant parties involved in the QRM activities ;
- facilitate the transfer of process knowledge and product development history to ease product progression along the life-cycle and to supplement already available knowledge about the product;
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance (4-7). The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the QRM process is to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

As FPP development progresses, in addition to supporting that development, the purpose of the QRM process is to determine and manage risks to bioavailability, safety, efficacy and product quality. QRM in development should differentiate process parameters (PPs) and quality attributes (QAs) from critical process parameters (CPPs) and critical quality

attributes (CQAs), thereby contributing to the defining and refining of the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and, where required with external stakeholders, such as MRAs. A very important aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and also possess a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, for the purposes of process validation as an example, would be hugely beneficial.

Finally, it should be noted that QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP. The existence and effectiveness of the relevant aspects of good clinical practices (GCP), good laboratory practices (GLP) and GMP should also be assessed when performing QRM activities.

2. QRM PROCESS

2.1 Initiating a QRM process

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk.



Possible steps used to initiate and plan a QRM process might include the following (Ref. ICH Q9):

- define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- identify a leader and necessary resources; and
- specify a timeline, deliverables and appropriate level of decision-making for the risk management process.

2.2 Personnel involved in QRM

The implementing party, i.e. pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team according to guidance in section 3.2.

The personnel should be able to:

- (a) conduct a risk analysis;
- (b) identify and analyse potential risks;
- (c) identify, evaluate risks and determine which ones should be controlled and which ones can be accepted;
- (d) recommend and implement adequate risk control measures;
- (e) devise procedures for risk review, monitoring and verification.

The objectives and scope of the QRM activities should be clearly defined. The scope should describe the segment of the process involved.

2.3 Knowledge of the product and process

Any activity of QRM would need to be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

Where necessary, a flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

2.4 Risk assessment

When risk assessment is conducted safety and efficacy need to be considered in addition to the quality concerns.

During the assessment all the risks that may be reasonably expected to occur in the activity under evaluation should be listed. This is usually applied during its initiation when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough risk analysis is required to ensure an effective risk control. It should review the materials, activities, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which



may be introduced, increased or controlled in each step should be drawn up. In the risk analysis the following basic questions should be addressed:

- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which potential risks should be addressed by the QRM activities and what control measures, if any, should be implemented for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure.

Options for risk assessment methodologies are described in section 5.

Risk assessment can be facilitated by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5 of this guidance.

Normally, potential risks in relation to the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;

- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel - human error;
- utilities;
- supply chain.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 5). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If supported by factual evidence it should be more obvious what mitigating action is required - the mitigating action is as important as the score assigned. Professional judgment should be used in interpretation of factual evidence but must be subject to justification.

Records of risk assessments should be maintained according to the document management system (see also 2.8).

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. Risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient is an unacceptable practice (10).

2.5 Risk control

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a



fundamental level its purpose is to reduce the risk to an acceptable level.

During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation which may be required, if any, for such controls.

If risk assessments are conducted and risk controls are employed they should be documented, subject to change control. If conducted for an ongoing activity it should be subject to periodic review and the frequency of review should be appropriate for the nature of the activity.

Specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks. These actions should ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures.

Specific corrective actions should be developed in advance for each identified risk including what is to be done when a deviation

occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken.

2.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

2.7 Verification of QRM process and methodologies

The established QRM process and methodologies need to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

- (a) review of the QRM process and its records;
- (b) review of deviations and product dispositions;



- (c) confirmation that identified risks is kept under control.

Initial verification of the planned QRM activities is necessary to determine whether it is scientifically and technically sound, that all risks have been identified and that, if the QRM activities are properly completed, these risks will be effectively controlled.

Information reviewed to verify the QRM process should include:

- (a) expert advice and scientific studies;
- (b) in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs or new risks are recognized. Where possible verification should include actions to confirm the efficacy of all elements of the QRM activities.

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow diagrams and appropriate records of the operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed in order to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies the QRM process should be modified as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

2.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. By ensuring that key stakeholders are engaged in both the data collection process for the risk assessment and the decision-making for risk control, this will ensure commitment and support for the QRM. The output of the QRM process and associated risk analysis justifying the approach should be documented and endorsed by the organization's quality unit and management. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.

There should be a report for every risk assessment, but the level of effort, formality and documentation will commensurate with the level of risk (2).

Regarding conclusions to a risk assessment the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow the process being assessed before the product reaches the patient (2).

It is expected that risk mitigation plans are identified and implemented where any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess



if risk assessments underrate the likelihood of occurrence and consequences of overrating detection such that the patient risk is underestimated. The factual evidence behind statements should be robust to challenge by inspectors.

All risk assessments performed by an organization should be documented for the purposes of inspection. This should list and track all key risks as perceived by the organization and summarize how these have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be maintained. A management process should be in place to review QRM – this may be incorporated into the quality management review process.

3. QRM APPLICATION FOR PHARMACEUTICALS

3.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and be appropriately resourced to enable the effective practice of the QRM principles.

In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all involved in these activities. Specific training should be provided as required to enhance awareness. Staff which has responsibility for managing and reviewing risks should receive formal training in the relevant procedures. Cooperation between producers, traders

and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of QRM depends on educating and training of management and employees in the importance of QRM in producing and supplying safe pharmaceuticals.

3.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities for all staff involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel. For example, one may consider the use of techniques such as RACI (responsibility/accountability/consulted/informed) grids to illustrate a more complete picture of the communication pathways.

The pharmaceutical manufacturer should assure that appropriate knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific



expertise or knowledge. Their role should be justifiable and clearly defined and resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved to lead or participate in risk assessments, e.g. a contract authorized person. The extent of involvement and responsibility/accountability must be documented in a technical agreement or other equivalent document between the individual and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of their organization and ensuring that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources to progress the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

3.3 QRM application during product development

The application of QRM procedures evolves through the various stages in development of a product.

It is important, where possible, to identify risks in the early phases of product development that could challenge the achievement of the QTPP. The first QRM exercise should be performed once the QTPP is defined and preformulation work on the drug candidate is

complete. For this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation.

These might include:

- cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- flowcharts (e.g. input-process-output (IPO));
- decision-trees;
- fault-tree analysis; and
- relationship matrices.

As the product progresses to later stage development, a more detailed analysis of the risks associated with both the API and FPP becomes a requirement. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances more detailed QRM exercises can be considered, concentrating on areas considered to be higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.



3.4 QRM application during validation and qualification

In keeping with the principles of QRM, this guideline recommends that process validation embraces the product life cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the development process into full-scale production that will provide a science-based assurance of consistent delivery of quality product in the production operation (10, 11, 12).

An important emphasis is that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product/process development through to the commercial production phase at which time the API and drug product CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches just serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all identified critical sources of variability. Any unplanned variations within a batch or between batches should be evaluated accordingly, employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches

that needs to be made depends on the depth of knowledge about the process.

For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company/MRA dialogue to agree on requirements for a regulatory submission. Until new approaches to demonstrate validation mature and become widely used, the traditional three-batch approach to validate a process is still acceptable. When applicable the principles of QRM should also be applied for qualification activities.

Qualification includes four stages (design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) but most frequently, only IQ, OQ and PQ are performed by manufacturers. QRM principles can be used to narrow the scope of IQ, OQ and PQ to cover only the essential elements that can affect product quality. It can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification.

Most importantly, by the time that a product is ready for commercialization, the manufacturing company will be expected to have derived sufficient knowledge of the commercial production process to support that commercialization to the optimized benefit of and minimized risk to the patient.

3.5 QRM application during commercial manufacturing

QRM principles applied as a process supports science-based and practical decisions when integrated into commercial manufacturing. In general implementing QRM should not



obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings, inspection commitments, etc.). All QRM activities should be structured in a way that allows escalation of risks to the appropriate management level within the organization.

Special focus can be on the risk assessment and risk control of, e.g:

- product quality risks;
- adverse impact to patient health based on product quality defects;
- product supply interruption to patients;
- GMP and regulatory compliance risks;
- multisite risks;
- multiproduct risks;
- new facility and changes to existing facility, e.g. start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

After completion of the risk assessment and risk control activities the outcomes must be summarized and communicated. The results may be documented in a new or existing report or they may be included as part of another document approved by appropriate decision-makers (e.g. site or functional management, system owner, quality unit, etc.). A risk review is important if new risks or changes to existing risk levels are identified through planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies/deviations, data monitoring, trends, inspections/audits, changes in regulatory environment, etc.

Risk review may also include evaluation of, e.g:

- effectiveness of risk control activities and actions;
- changes in observed risk levels or existing controls.

In principal there are two focuses when implementing QRM in commercial manufacturing: a system focus and a product focus.

3.5.1 QRM integration with key quality system elements

Effective QRM can facilitate the “What to do?” and, therefore, support better and more informed decisions. QRM should be integrated into existing quality system elements and related business processes and documented appropriately.

Situations in which the use of the QRM process might provide information are beneficial in a variety of operations, e.g:

- integrated quality management: documentation; training and education; quality defects; auditing/inspection; change management/change control (includes equipment, facilities, utilities, control and IT systems); continual improvement/corrective and preventive actions (CAPA);
- facilities, equipment and utilities: e.g. design; qualification; maintenance and decommissioning of facility/equipment; hygiene aspects; cleaning of equipment and environmental control; calibration/preventive maintenance; computer



systems and computer-controlled equipment;

- supplier, materials and contract service management: e.g. assessment and evaluation of suppliers and contract manufacturers; starting material; use of materials; storage; logistics and distribution conditions;
- technology transfer: e.g. from development to manufacturing; during commercial manufacturing between sites; from commercial manufacturing to product discontinuation.

3.5.2 QRM application in product manufacturing operations

Effective QRM can facilitate the “How to do?” and, therefore, ensure products will meet acceptable standards for safety, quality, and compliance.

QRM methodology can support, beside others, the following events to assess and control quality risks, e.g:

- production: e.g. manufacturing process risks; validation; in-process sampling and testing controls; production planning; deviation and investigation management; change management;
- laboratory control and stability studies: e.g. out-of-specification results; retest period/expiration date; method transfers;

- packaging and labelling: e.g. design of packages; selection of container-closure system; label controls;
- storage, transport and distribution: e.g. cold chain.

4. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES(2, 9)

4.1 Introduction

A key principle of this guideline is that all MRAs, developing country manufacturing sites and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews, etc.).

Equally, it is recommended that QRM be applied by the MRAs themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resource commensurate with their perceived significance of risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

4.2 QRM application to inspection strategy

4.2.1 Risk management in inspections

The inspection section or unit of a medicines regulatory authority should operate within a written, implemented quality management system (13). Standard operating procedures (SOPs) should be followed for activities



including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a risk management plan (RMP) that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a rolling basis, or at least annually and should cover all types of inspections (including GMP, GCP, GLP) and other activities.

Appropriate risk assessment tools should be used in the process, and the risk assessment for a site to be inspected should be documented in a risk assessment worksheet. Records should be maintained.

A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

4.2.2 Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product risk and patient risk.

Risk rating should normally be done only for sites that had been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that had not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where in addition appropriate evidence of GXP compliance is available that indicates that there is no or acceptable low risk to products and patients.

Various factors should be considered in the risk assessment exercise, and may be different for the different types of GXP inspections.

Risk factors to be considered depend on the type of inspection, and may include:

- (a) outcome of inspection by another regulatory authority;
- (b) outcome of the previous inspection;
- (c) complexity of the site (e.g. buildings, utilities);
- (d) complexity of the product (e.g. sterile, non-sterile);
- (e) type of product (e.g. biological, low dose);
- (f) complaints and recalls;
- (g) significance of changes (e.g. equipment, key personnel);
- (h) results of product testing;
- (i) risk to the patient;
- (j) complex route of synthesis (API);
- (k) polymorphism (API);
- (l) biopharmaceutical classification of the product;

The number of inspectors and number of days required for the inspection, as well as the scope of the inspection, should be determined based on the risk rating of the site inspection.

Inspection reports should contain findings and observations. Departures from GXP should be classified where appropriate, as “critical, major or minor”.

The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in relation to the nature of the observation as well as the number of occurrences.



4.2.3 Corrective action and preventive action review, and scheduling of routine inspections

Corrective actions and preventive actions (CAPA) should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report.

Based on the inspection outcome and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded.

Inspection frequency should be defined based on the risk rating. For example, a frequency can be defined as every 6, 12, 18 or 24 months. (The maximum time interval should be no more than every 36 months.)

4.2.4 Complaint handling and investigation

Handling and investigation of quality complaints should be done in accordance with a written SOP.

The scope and depth of the investigation (including whether a desk review or on-site inspection will be done) should be based on risk assessment.

4.3 Inspection of QRM at a manufacturing site

Note. During inspections, inspectors should assess whether a manufacturer has appropriate skills, scientific knowledge as well as product and process knowledge for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties.

The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system.

It should cover at least the following areas:

- (a) general approach to both planned and unplanned risk assessment – and include scope, responsibilities, controls, approvals, management systems, applicability and exclusions;
- (b) personnel with appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined;
- (c) senior management should be involved in the identification and implementation of QRM principles within the company;
- (d) the risk management procedure(s) for each area of application should be clearly defined;
- (e) quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.

The procedure for risk management should be implemented. Manufacturers should identify significant risks and consider all the relevant data from reliable sources.

Personnel should be trained and assessed in the principles of QRM.

Where appropriate, a team of members of personnel should participate in the QRM processes.



The level of effort and resources used in risk assessment should be appropriate to the importance of the identified problem. Critical issues should be addressed with appropriate urgency and formality.

There should be a logical selection of tools for risk assessment. Risk acceptance criteria should be appropriate. Risk assessments should not underrate the severity, nor overrate detection of occurrences resulting in underestimating patient risk.

The risk acceptance criteria should be appropriate for the specific situation in question.

Risk controls should be effective. The company should have a review programme to measure the efficiency of the measures taken.

Risk-based decision(s) should be science-based and concordant with the predefined acceptance criteria.

All documentation related to the QRM activities should be completed in a reasonable time frame and should be accessible.

Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.

4.4 QRM applied to dossier review (assessment)

NMRA assessment processes rely on QRM principles in the management of resources (time and assessors), as well as in the management of product-related risk factors. Efficient management of resources minimizes the risk that limited resources are not used to best effect, and ultimately ensures that important products are available in a timely manner. Key factors to be considered include

the prioritization of dossiers, the screening process, identification of the specific risk factors inherent for a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the lifecycle of the product, for example through effective communication between assessors and inspectors, and by establishing systems for dealing with the products after approval.

The prioritization of dossiers should consider the therapeutic needs of the regional population (disease occurrence, the need for paediatric formulations, combination products, etc.) and the availability of medicines on the market. Prioritization should be a dynamic process in order to accommodate emerging issues such as pandemics. Other considerations related to prioritization based on medical need may include fixed-dose combinations versus single-ingredient or co-packaged products, extended release products versus twice or thrice daily dosing products, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids.

The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness are entered into the full assessment process. Insufficient screening processes allow a lower standard of quality of dossiers to be accepted for review, significantly increasing assessment time.

Identification of dossier related and product related risk factors allows for the allocation of proper resources to specific dossiers. Possible risk factors include the experience and track record of the manufacturer, narrow



therapeutic range products, sterile versus non-sterile APIs and products, API related considerations such as semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities, and product related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (modified release, transdermal products, inhalation products, etc.). Once risk factors are identified, resources should be allocated to minimize risk, for example assessors with expertise related to the identified product-related risk should be assigned to assess the dossier whenever possible.

When resources allow, organization of assessors may be done according to specialization, assigning assessors into various product categories (e.g. generic products, sterile products, solid oral dosage forms, special delivery systems, etc.). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and directed to the appropriate expertise. Where a high level of risk is identified for a dossier, assignment of more experienced assessors is required, at minimum on a consultative basis.

The risk level associated with a dossier may change during the course of assessment, for example rejection of the bioequivalence study will result in additional time required to conduct and assess additional studies and associated additional quality information. In such a scenario the risk relates both to the use of additional resources and to increased risk that the overall product quality may be poor.

Allocation of resources to various aspects/ sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate to the associated risk level. An understanding of the relative criticality of dossier sections or aspects is necessary for efficient use of resources. All aspects of the dossier are important to achieve overall quality, safety and efficacy, however some areas are inherently more critical from a risk perspective and warrant more time in the assessment process. Examples include the clinical/bioavailability reviews, API synthesis, specifications and stability studies, FPP manufacturing details, pharmaceutical development studies including biowaiver justification, process validation, specifications and stability studies. An example for most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging, compared to the time allotted to review the packaging process. During the assessment process there should be a standard procedure to communicate to inspectors those identified issues which may require consideration during inspection. After approval of a product, QRM principles should be applied to evaluate the impact of proposed variations or changes. A clear guideline that outlines possible post-approval changes and assigns an associated risk level is an effective means to achieve this.

5. RISK MANAGEMENT TOOLS

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6, 8); neither list is exhaustive.



The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (10) of common RM principles and best practices, several working tools to foster consistency in the use of ICH Q9 (6) in day-to-day RM decision-making, and a series of examples of RM applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA) (14, 15, 16), hazard operability analysis (HAZOP) (17) and HACCP (3)

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of identified risks during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words, how likely is it to happen and how severe would it be if it did happen. Impact and probability can each be classified, e.g. into 5 levels (1-5) or with a weighting towards the higher probability and impact ratings (e.g. 1,3,5,7,10, etc.), so that a grid or matrix can be constructed.

Table 1. An example of a probability versus impact matrix

Probability	Impact				
	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table 2.

**Table 2. Example of a consequences table for probability and impact**

Score	Probability	Example	Score	Impact	Consequence
1	Rare	<ul style="list-style-type: none">• Seen every 10-30 years	1	Negligible	<ul style="list-style-type: none">• No regulatory issue• No effect on and not noticeable by patient
2	Unlikely	<ul style="list-style-type: none">• Seen every 5-10 years	2	Marginal	<ul style="list-style-type: none">• May require MRA notification• Decision to release product not compromised
3	Possible	<ul style="list-style-type: none">• Seen every 1-5 years	3	Moderate	<ul style="list-style-type: none">• MRA inspection may identify a major concern but deficiency quite easily resolved• Limited product recall possible
4	Likely	<ul style="list-style-type: none">• Seen to occur more than once a year	4	Critical	<ul style="list-style-type: none">• MRA inspection may conclude serious non-compliance• Likely product recall from one or more markets
5	Almost certain	<ul style="list-style-type: none">• Seen several times a year	5	Catastrophic	<ul style="list-style-type: none">• Enforcement action by MRA such as consent decree, product seizure• Global product recall

This table is just a very basic example and would need to be customized for the specific process in question to enable better and practical definition of the consequence categories. It should be cautioned that the value of a risk matrix does very much rely upon input information and should only be used by staff with a good understanding of the embedded judgments and, as such, the resolution of low/medium/high categorization.

As a summary of the common, well-recognized QRM tool options available for the purposes of this guideline, the following table has been based on the one from the PQRI-MTC report (10). The list is not comprehensive but it does include some of the more frequently used approaches.

**Table 3. Examples of common risk management tools (based on 10)**

Risk management tool	Description/attributes	Potential applications
Basic tools		
Diagram analysis <ul style="list-style-type: none">• Flowcharts• Check sheets• Process mapping• Cause/effect diagrams	<ul style="list-style-type: none">• Simple techniques that are commonly used to gather and organize data, structure RM processes and facilitate decision-making	<ul style="list-style-type: none">• Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filtering	<ul style="list-style-type: none">• Method to compare and rank risks• Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk,• and weighting factors and risk score	<ul style="list-style-type: none">• Prioritize operating areas or sites for audit/assessment• Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA)	<ul style="list-style-type: none">• Method used to identify all root causes of an assumed failure or problem• Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains• Relies heavily on full process understanding to identify causal factors	<ul style="list-style-type: none">• Investigate product complaints• Evaluate deviations



Hazard operability analysis (HAZOP)	<ul style="list-style-type: none">• Tool assumes that risk events are caused by deviations from the design and operating intentions• Uses a systematic technique to help identify potential deviations from normal use or design intentions	<ul style="list-style-type: none">• Access manufacturing processes, suppliers, facilities and equipment• Commonly used to evaluate process safety hazards
Hazards analysis and critical control points (HACCP)	<ul style="list-style-type: none">• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring• Bottom-up approach that considers how to prevent hazards from occurring and/or propagating• Emphasizes strength of preventative controls rather than ability to detect	<ul style="list-style-type: none">• Better for preventative applications rather than reactive• Great precursor or complement to process validation• Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none">• Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that CPPs will be met.• Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance• Once failure modes are known, risk reduction actions can be applied to eliminate, reduce or control potential failures• Highly dependent upon strong understanding of product, process and/or facility under evaluation• Output is a relative “risk score” for each failure mode	<ul style="list-style-type: none">• Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps and/or critical parameters

[Note from the Secretariat: the authors will be contacted regarding copyright of the above table.]



Another general overview of and references for some of the risk tools that might be brought to bear in QRM by industry and regulators is provided in Annex 20 (Annex I) of the EU GMP guideline (2).

6. GLOSSARY

[Note from the secretariat: Glossary will be double-checked against the most up-to-date definitions in the final version.]

Control strategy (source: ICH Q8)

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

Critical quality attribute (CQA) (source: ICH Q8)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

Formal experimental design (source: ICH Q8)

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

Pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements

Planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

Process robustness (source: ICH Q8)

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Product quality research institute (PQRI)

A collaborative process involving the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research



(CDER), industry and academia. The mission of PQRI is to conduct research to generate specific scientific information that should be submitted in a regulatory filing to CDER (but which will be worth consideration for all MRAs).

PQRI member organizations, representing industry, academia, and government, cover a wide array of scientific issues related to pharmaceutical products. Through its working groups and technical committees, PQRI tackles projects to ensure the quality, safety and performance of drug products and produces publications for the public domain based upon the output of those projects.

Qualification

Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

Quality critical process parameter (source: ICH Q8)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

Stakeholder

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, healthcare professional, MRAs and the pharmaceutical industry.

Unplanned risk assessment

An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

Validation

The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes-including equipment, buildings, personnel and materials are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

Verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.



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ANNEX 9: ACTIVE PHARMACEUTICAL INGREDIENTS

1. INTRODUCTION

1.1 Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide “manufacturing” includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant annexes to the GMP Guide, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

The GMP Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, or aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration requirements or modify pharmacopoeial requirements and does not affect the ability of the responsible competent authority to establish specific registration requirements regarding APIs within the context of marketing/manufacturing authorizations.

All commitments in registration documents must be met.

1.2 Scope

This Guide applies to the manufacture of APIs for medicinal products for both human and veterinary use. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in national legislations and interpreted in the GMP Guide including its Annex1.

In the case of ecto-parasiticides for veterinary use, other standards than this Guide, that ensure that the material is of appropriate quality, may be used.

This Guide excludes whole blood and plasmas the PIC/S GMP Guide for Blood Establishments lays down the detailed requirements for the collection and testing of blood. However, it does include APIs that are produced using blood or plasma as raw materials. Finally, the Guide does not apply to bulk-packaged medicinal products.

It applies to all other active starting materials subject to any derogations described in the annexes to the GMP Guide, in particular Annexes 2 to 7 where supplementary guidance for certain types of API may be found. The annexes will consequently undergo a review but in the meantime and only until this review is complete, manufacturers may choose to continue to use Part I of the basic requirements and the relevant annexes for products covered by those annexes, or may already apply Part II.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of investigational medicinal products although it should be noted



that its application in this case, although recommended, is not required in PIC/S countries.

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.

The manufacturer should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps showing ray in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".

**Table1: Application of this Guide to API Manufacturing**

Type of Manufacturing	Application of this Guide to steps (show in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements



2. QUALITY MANAGEMENT

2.1 Principles

- 2.10 Quality should be the responsibility of all persons involved in manufacturing.
- 2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.
- 2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.
- 2.13 There should be a quality unit(s) that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.
- 2.14 The persons authorized to release intermediates and APIs should be specified.
- 2.15 All quality related activities should be recorded at the time they are performed.

- 2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.
- 2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit (s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).
- 2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

2.2 Responsibilities of the Quality Unit(s)

- 2.20 The quality unit(s) should be involved in all quality-related matters.
- 2.21 The quality unit(s) should review and approve all appropriate quality-related documents.
- 2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:



1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
4. Making sure that critical deviations are investigated and resolved;
5. Approving all specifications and master production Instructions;
6. Approving all procedures impacting the quality of Intermediates or APIs;
7. Making sure that internal audits (self-inspections) are Performed;
8. Approving intermediate and API contract manufacturers;
9. Approving changes that potentially impact intermediate or API Quality;
10. Reviewing and approving validation protocols and reports;
11. making sure that quality related complaints are investigated and resolved;
12. making sure those effective systems are used for maintaining and calibrating critical equipment;

13. Making sure that materials are appropriately tested and the results are reported;
14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
15. Performing product quality reviews (as defined in Section 2.5)

2.3 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
2. Producing APIs and, when appropriate, intermediates according to pre- approved instructions;
3. Reviewing all production batch records and ensuring that these are completed and signed;
4. making sure that all production deviations are reported and evaluated and that critical deviation are investigated and the conclusions are recorded;
5. making sure that production facilities are clean and when appropriate disinfected;



6. making sure that the necessary calibrations are performed and records kept;
 7. making sure that the premises and equipment are maintained and records kept;
 8. making sure that validation protocols and reports are reviewed and approved;
 9. Evaluating proposed changes in product, processor Equipment; and
 10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.
- 2.4 Internal Audits (Self Inspection)**
- 2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.
 - 2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.
- 2.5 Product Quality Review**
- 2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:
 - A review of critical in-process control and critical API test results;
 - A review of all batches that failed to meet established specification(s);
 - A review of all critical deviations or non-conformances and related investigations;
 - A review of any changes carried out to the processes or analytical methods;
 - A review of results of the stability monitoring program;
 - A review of all quality-related returns, complaints and recalls; and
 - A review of adequacy of corrective actions.
- 2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.
- 3. PERSONNEL**
- 3.1 Personnel Qualifications**
- 3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.
 - 3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.



3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have

an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. BUILDINGS AND FACILITIES

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit



- exposure to objectionable microbiological contaminants as appropriate.
- 4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.
- 4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.
- 4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.
- 4.14 There should be defined areas or other control systems for the following activities:
- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
 - Quarantine before release or rejection of intermediates and APIs;
 - Sampling of intermediates and APIs;
 - Holding rejected materials before further disposition (e.g., return, reprocessing or destruction);
 - Storage of released materials;
 - Production operations;
 - Packaging and labelling operations; and
 - Laboratory operations.
- 4.15 Adequate, clean washing and toilet facilities should be provided for personnel.
- These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air-driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.
- 4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.
- ## 4.2 Utilities
- 4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
- 4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include



equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipe work should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipe work should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, Meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or

microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated in activation and/or cleaning procedures are established and maintained.



- 4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.
- 4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.
- 4.5 Lighting**
- 4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.
- 4.6 Sewage and Refuse**
- 4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from building and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.
- 4.7 Sanitation and Maintenance**
- 4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.
- 4.71 Written procedures should be established as signing responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.
- 4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.
- 5. PROCESS EQUIPMENT**
- 5.1 Design and Construction**
- 5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.
- 5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.
- 5.12 Production equipment should only be used within its qualified operating range.
- 5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing



- lines used during the production of an intermediate or API should be appropriately identified.
- 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.
- 5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
- 5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).
- 5.2 Equipment Maintenance and Cleaning**
- 5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.
- 5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:
- Assignment of responsibility for cleaning of equipment;
 - Cleaning schedules, including, where appropriate, sanitizing schedules;
 - A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
 - When appropriate, instructions for disassembling and re assembling each article of equipment to ensure proper cleaning;
 - Instructions for the removal or obliteration of previous batch identification;
 - Instructions for the protection of clean equipment from contamination prior to use;
 - Inspection of equipment for cleanliness immediately before use, if practical; and
 - Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.
- 5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.
- 5.23 Where equipment is assigned to continuous production or



- campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).
- 5.24 Non-dedicated equipment should be cleaned between productions of different materials to prevent cross-contamination.
- 5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
- 5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.
- 5.3 Calibration**
- 5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.
- 5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.
- 5.32 Records of these calibrations should be maintained.
- 5.33 The current calibration status of critical equipment should be known and verifiable.
- 5.34 Instruments that do not meet calibration criteria should not be used.
- 5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.
- 5.4 Computerized Systems**
- 5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
- 5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- 5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.
- 5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and not captured). There should be a record of any



- data change made, the previous entry, who made the change, and when the change was made.
- 5.44 Written procedures should be available for the operation and maintenance of computerized systems.
- 5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
- 5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or there liability of records or test results should be recorded and investigated.
- 5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.
- 5.48 If system break downs or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.
- 5.49 Data can be recorded by a second means in addition to the computer system.
- ## 6. DOCUMENTATION AND RECORDS
- ### 6.1 Documentation System and Specifications
- 6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.
- 6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.
- 6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.
- 6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained or at least 3 years after the batch is completely distributed.



- 6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.
- 6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
- 6.16 Specifications, instructions, procedures, and record scan be retained either as originals or as true copies such as photocopies, micro film, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.
- 6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.
- 6.18 If electronic signatures are used on documents, they should be authenticated and secure.
- 6.2 Equipment Cleaning and Use Record**
- 6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time(if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
- 6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, there cords of cleaning, maintenance, and use can be part of the batch record or maintained separately.
- 6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials**
- 6.30 Records should be maintained including:
- The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's; the name of the supplier; the



- supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
 - The results of any test or examination performed and the conclusions derived from this;
 - Records tracing the use of materials;
 - Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and
 - the final decision regarding rejected raw materials, intermediates or API Labelling and packaging materials.
- 6.31 Master (approved) labels should be maintained for comparison to issued labels.
- 6.4 Master Production Instructions (Master Production and Control Records)**
- 6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).
- 6.41 Master production instructions should include:
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
 - an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be provided they are justified;
 - The production location and major production equipment to be used;
 - Detailed production instructions, including the:
 - Sequences to be followed,
 - ranges of process parameters to be used,
 - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
 - time limits for completion of individual processing steps and/or the total process, where appropriate; and
 - expected yield ranges at appropriate phases of processing or time;
 - Where appropriate, special notations and precautions to be followed, or cross-references to these; and



- the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.
- 6.5 Batch Production Records (Batch Production and Control Records)**
- 6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.
- 6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.
- 6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:
- Dates and, when appropriate, times;
 - Identity of major equipment (e.g., reactors, driers, mills, etc.) used;
 - Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed Materials used during manufacturing;
 - Actual results recorded for critical process parameters;
 - any sampling performed;
 - Signatures of the persons performing and directly supervising or checking each critical step in the operation;
 - In-process and laboratory test results;
 - Actual yield at appropriate phases or times;
 - Description of packaging and label for intermediate or API;
 - Representative label of API or intermediate if made commercially available;
 - any deviation noted, its evaluation, investigation conducted (if Appropriate) or reference to that investigation if stored separately; and
 - Results of release testing.



6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory Control Records

6.60 Laboratory control record should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
- A statement of or reference to each test method used;
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions,
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified

to show the specific material and batch tested;

- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- A statement of the test results and how they compare with established acceptance criteria;
- The signature of the person who performed each test and the date(s) the tests were performed; and
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

6.61 Complete records should also be maintained for:

- any modifications to an established analytical method,
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch



- production and laboratory control records, including;
- Packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.
- 6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).
- 6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.
- 6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.
- 7. MATERIALS MANAGEMENT**
- 7.1 General Controls**
- 7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.
- 7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.
- 7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).
- 7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.
- 7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.
- 7.2 Receipt and Quarantine**
- 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.
- 7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released.



- Procedures should be available to prevent discharging in coming materials wrongly into the existing stock.
- 7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker.
- Means of providing this assurance could include one or more of the following:
- certificate of cleaning
 - testing for trace impurities
 - audit of the supplier.
- 7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.
- 7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.
- 7.3 Sampling and Testing of Incoming Production Materials**
- 7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.
- 7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.
- 7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.
- 7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan



that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

8. PRODUCTION AND IN - PROCESS CONTROLS

7.4 Storage

8.1 Production Operations

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

- Material name and/or item code;
- Receiving or control number;
- Weight or measure of material in the new container; and
- Re-evaluation or retest date if appropriate.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

8.12 Critical weighing, measuring, or subdividing operations should



be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

- 8.13 Other critical activities should be witnessed or subjected to an equivalent control.
- 8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.
- 8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.
- 8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.
- 8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time Limits

- 8.20 If time limits are specified in the master production instruction

(see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be in appropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

- 8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

- 8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
- 8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate



- for later processing steps (e.g., isolation and purification steps).
- 8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should best put in writing and approved by the quality unit(s).
- 8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made with in pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.
- 8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.
- 8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.
- 8.36 Out-of-specification (OOS) investigations are not normally needed for in- process tests that are performed for the purpose of monitoring and/or adjusting the process.
- 8.4 Blending Batches of Intermediates or APIs
- 8.40 For the purpose of this document, blending is defined as the process of combining materials with in the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch)or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.
- 8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 8.42 Acceptable blending operations include but are not limited to:
- blending of small batches to increase batch size
 - Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.
- 8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for



conformance to established specifications where appropriate.

- 8.44 The batch record of the blending process should allow traceability back to the individual batches that makeup the blend.
- 8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.
- 8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.
- 8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination Control

- 8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and in complete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such

carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

- 8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.
- 8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. PACKAGING AND IDENTIFICATION LABELLING OF APIS AND INTERMEDIATES

9.1 General

- 9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.
- 9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
- 9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.



9.2 Packaging Materials

- 9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.
- 9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.
- 9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label Issuance and Control

- 9.30 Access to the label storage areas should be limited to authorized personnel.
- 9.31 Procedures should be used to reconcile the quantities of labels is sued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit (s).
- 9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed.

Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

- 9.33 Obsolete and outdated labels should be destroyed.
- 9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
- 9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
- 9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and Labelling Operations

- 9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.
- 9.41 Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.
- 9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the



product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, there test date should be indicated on the label and/or Certificate of Analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside of the

manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. STORAGE AND DISTRIBUTION

10.1 Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the un intentional or un authorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate



- controls and documentation are in place.
- 10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.
- 10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.
- 10.23 The manufacturer should ensure that the contract accept or (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.
- 10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.
- 11. LABORATORY CONTROLS**
- 11.1 General Controls**
- 11.10 The independent quality unit (s) should have at its disposal adequate laboratory facilities.
- 11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.
- 11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).
- 11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins; appropriate action limits should be established and met.
- 11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.



- 11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.
- 11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.
- 11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.
- 11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established.
- 11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically prequalified in accordance with a written protocol.
- 11.2 Testing of Intermediates and APIs**
- 11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.
- 11.21 An impurity profile describing the identified and un identified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. Retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not



- necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.
- 11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- 11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.
- 11.3 Validation of Analytical Procedures-see Section 12.**
- 11.4 Certificates of Analysis**
- 11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.
- 11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.
- 11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).
- 11.43 Certificates should be dated and signed by authorized personnel of the quality unit (s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a re-packer or re-processor, the Certificate of Analysis should show the name, address and telephone number of the re-packer/reprocess or and a reference to the name of the original manufacturer.
- 11.44 If new Certificates are issued by or on behalf of re-packers/re-processors, agents' or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.
- 11.5 Stability Monitoring of APIs**
- 11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.



- 11.51 The test procedures used in stability testing should be validated and be stability indicating.
- 11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
- 11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm their test or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.
- 11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.
- 11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of
- specific test intervals (e.g. 9 month testing) can be considered.
- 11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.
- 11.6 Expiry and Retest Dating**
- 11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).
- 11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.
- 11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.
- 11.63 A representative sample should be taken for the purpose of performing a retest.
- 11.7 Reserve/Retention Samples**
- 11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the



quality of batches of API and not for future stability testing purposes.

validation phase, should be documented.

11.71 Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

- defining the API in terms of its critical product attributes;
- identifying process parameters that could affect the critical quality attributes of the API;
- determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12.2 Validation Documentation

12. VALIDATION

12.1 Validation Policy

12.20 Written validation protocols should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit (s) and other designated units.

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.



12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting processes validation activities, appropriate qualification of critical equipment and ancillary systems should be completed.

Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as

intended throughout the anticipated operating ranges.

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced in



- frequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.
- 12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:
- (1) Critical quality attributes and critical process parameters have been identified;
 - (2) Appropriate in-process acceptance criteria and controls have been established;
 - (3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and
 - (4) Impurity profiles have been established for the existing API.
- 12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested
- to obtain data to retrospectively validate the process.
- 12.5 Process Validation Program**
- 12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.
- 12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.
- 12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or



- for batches used for pivotal clinical and toxicological studies.
- 12.6 Periodic Review of Validated Systems**
- 12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.
- 12.7 Cleaning Validation**
- 12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.
- 12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning
- and the calculation of residue limits based on potency, toxicity, and stability.
- 12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods.
- The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.
- 12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).
- 12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery



- level should be established. Residue limits should be practical, achievable, and verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.
- 12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).
- 12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.
- 12.8 Validation of Analytical Methods**
- 12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.
- 12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.
- 12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.
- 12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.
- 13. CHANGE CONTROL**
- 13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
- 13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer



- hardware), processing steps, labelling and packaging materials, and computer software.
- 13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit (s).
- 13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process.
- Changes can be classified (e.g.as minor or major) depending on the nature and extent of the changes, and the effects these changes may impact on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.
- 13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
- 13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.
- 13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.
- 13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.
- ## 14. REJECTION AND RE-USE OF MATERIALS
- ### 14.1 Rejection
- 14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.
- ### 14.2 Reprocessing
- 14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such



- reprocessing should be included as part of the standard manufacturing process.
- 14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.
- 14.22 Introducing un reacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.
- 14.3 Reworking**
- 14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.
- 14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that there worked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define their work procedure, how it will be carried out,
- and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
- 14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.
- 14.4 Recovery of Materials and Solvents**
- 14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and there covered materials meet specifications suitable for their intended use.
- 14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.
- 14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.



14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

15. COMPLAINTS AND RECALLS

15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

- Name and address of complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Complaint nature (including name and batch number of the API);
- Date complaint is received;
- Action initially taken (including dates and identity of person taking the action);
- any follow-up action taken;
- Response provided to the originator of complaint (including date response sent); and
- Final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how are call should be initiated, who should be informed about the recall,



- and how the recalled material should be treated.
- 15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advices ought.
- 16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**
- 16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.
- 16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract accept or that defines in detail the GMP responsibilities, including the quality measures, of each party.
- 16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.
- 16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.
- 16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.
- 16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.
- 17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS AND RELABELLERS**
- 17.1 Applicability**
- 17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or intermediate.
- 17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this Guide.
- 17.2 Traceability of Distributed APIs and Intermediates**
- 17.20 Agents, brokers, traders, distributors, repackers, or relabellers



should maintain complete traceability of APIs and intermediates that they distribute.	17.41	Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.	
Documents that should be retained and available include:	17.5	Stability	
<ul style="list-style-type: none">• Identity of original manufacturer• Address of original manufacturer• Purchase orders• Bills of lading (transportation documentation)• Receipt documents• Name or designation of API or intermediate• Manufacturer's batch number• Transportation and distribution records• All authentic Certificates of Analysis, including those of the original manufacturer• Retest or expiry date	17.50	Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.	
17.3	Quality Management	17.6	Transfer of Information
17.30	Agents, brokers, traders, distributors, repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in Section 2.	17.60	Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer and from the customer to the API or intermediate manufacturer.
17.4	Repackaging, Relabelling and Holding of APIs and Intermediates	17.61	The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number (s) supplied.
17.40	Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.	17.62	The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this



- context “authorized” refers to authorized by the manufacturer.)
- 17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.
- 17.7 Handling of Complaints and Recalls**
- 17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.
- 17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation in to the cause for the complaint or recall should be conducted and documented by the appropriate party.
- 17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).
- 17.8 Handling of Returns**
- 17.80 Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.
- 18. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/ FERMENTATION**
- 18.1 General**
- 18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.



- 18.11 The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section.
- Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.
- 18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.
- 18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms.
- Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.
- 18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which avail of the cell bank is retrieved for use in manufacturing.
- 18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).
- 18.16 In general, process controls should take in to account:
- Maintenance of the Working Cell Bank (where appropriate);



- Proper inoculation and expansion of the culture;
 - Control of the critical operating parameters during fermentation/ cellculture;
 - Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
 - Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of microbiological nature) and from loss of quality;
 - Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
 - Viral safety concerns as described in ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.
- 18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.
- 18.2 Cell Bank Maintenance and Record Keeping**
- 18.20 Access to cell banks should be limited to authorized personnel.
- 18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.
- 18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.
- 18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.
- 18.24 See ICH Guideline Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/ Biological Products for a more complete discussion of cell banking.
- 18.3 Cell Culture/Fermentation**
- 18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculations of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.
- 18.31 Where the quality of the API can be affected by microbial contamination, manipulations



- using open vessels should be performed in a biosafety cabinet or similarly controlled environment.
- 18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.
- 18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.
- 18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.
- 18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.
- 18.36 There should be appropriate procedures in place to detect contamination and determines the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation
- processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.
- 18.37 Records of contamination events should be maintained.
- 18.38 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.
- 18.4 Harvesting, Isolation and Purification**
- 18.40 Harvesting steps either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment or are as designed to minimize the risk of contamination.
- 18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.



- 18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.
- 18.43 If open systems are used; purification should be performed under environmental conditions appropriate for the preservation of product quality.
- 18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.
- 18.5 Viral Removal/Inactivation Steps**
- 18.50 See the ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin for more specific information.
- 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.
- 18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/in-activation steps.
- Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.
- 18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.
- 19. APIs FOR USE IN CLINICAL TRIALS**
- 19.1 General**
- 19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.
- 19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

**19.2 Quality**

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit (s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations in to yield variations are not expected.

**19.6 Validation**

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or in exact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7 Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8 Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time

after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.



20. GLOSSARY

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment in to the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Batch (or Lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number)

A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden

The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bio burden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System

A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System

A process or operation integrated with a computer system.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

**Contract Manufacturer**

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination

Contamination of a material or product with another material or product.

Deviation

Departure from an approved instruction or established standard.

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance

See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity

Any component present in the intermediate or API that is not the desired entity.

Impurity Profile

A description of the identified and un identified impurities present in an API.

In-Process Control (or Process Control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot See Batch**Lot Number see Batch Number**

See Batch Number

Manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls.



Material

A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, APIs and packaging and labelling materials.

Mother Liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain un reacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

Packaging Material

Any material intended to protect an intermediate or API during storage and transport.

Procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API. Process Aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not they participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process Control See In-Process Control Production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)

Checking or testing that specifications are met.

Quality Unit (s)

An organizational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.



Reference Standard, Primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is in complete is considered to be part of the normal process, and not reprocessing.

Retest Date

The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed)

See definition for signed

Signed (signature)

The record of the individual who performed a particular action or review. This record can be initials, full hand written signature, personal seal, or authenticated and secure electronic signature.

Solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.



Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.



ANNEX 10: WASTE MANAGEMENT FOR MEDICINAL PRODUCT MANUFACTURERS

10.1 PURPOSE

These guidelines provide suggestions on how to manage pharmaceutical waste, maintaining and updating an inventory of pharmaceutical waste streams, managing waste storage sites, and disposing of waste material. Pharmaceutical waste that exhibits a characteristic of hazardous must be managed and disposed of separately.

10.2 SCOPE

There are two (2) categories of pharmaceutical waste that need to be managed and they are defined as follows:

Hazardous Waste: Waste pharmaceuticals that must be segregated and managed as such. These include antineoplastic agents, radioactive agents, hormonal products, penicillins, solvents from laboratory.

Non-Hazardous Pharmaceutical Waste: All other pharmaceutical waste not included in one above.

10.3 SOLID WASTE MATERIALS

- 10.3.1 Solid Waste (non- hazardous) - Garbage, refuse, sludge, industrial waste and other discarded materials. Solid waste management should predominantly regulated at the local level and be managed in accordance with local environmental regulations
- 10.3.2 The management of solid waste should involve its collection, transport, processing and recycling or disposal. Collection should include the gathering of solid waste and recyclable materials, and the transport of these materials, after collection, to the location where the collection vehicle is emptied. This location may be a material processing facility, a transfer station or a landfill disposal site.
- 10.3.3 Waste disposal can be done primarily by land filling or closure of existing dump sites. Modern sanitary landfills are not dumps; they are engineered facilities used for disposing of solid wastes on land without creating hazards to public health or safety,
- 10.3.4 Provision should be made for the proper and safe storage of waste materials awaiting disposal.
- 10.3.5 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.



10.4 LIQUID WASTE MATERIALS

- 10.4.1 If liquid effluent poses a safety or contamination risk, the effluent should be treated in Effluent Treatment Plant before being discharged to a municipal drain.
- 10.4.2 After treatment in ETP, water should be sampled for analysis (pH, Biochemical oxygen demand (B.O.D) and chemical oxygen demand (COD)) to check quality before being discharged to municipal drain.
- 10.4.3 Effluent treatment is the process of removing contaminants from waste water . It includes physical, chemical, and biological processes to remove physical, chemical and biological contaminants. Its objective is to produce an environmentally safe fluid waste stream (or treated effluent) and a solid waste (or treated sludge) suitable for disposal or reuse (usually as farm fertilizer).





PART THREE:

**GUIDELINES FOR PREPARATION
FOR SITE MASTER FILE FOR PHARMACEUTICAL
MANUFACTURING FACILITIES**



1. ABBREVIATIONS AND ACRONYMS

API	-	Active Pharmaceutical Ingredient
DUNS	-	Data Universal Numbering System
EAC	-	East Africa Community
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
GMP	-	Good Manufacturing Practices
GPS	-	Global Positioning System
HVAC	-	Heating Ventilation and Air Condition
PAT	-	Process Analytical Technology
PIC/S	-	Pharmaceutical Inspection Cooperation Scheme
QC	-	Quality Control
SMF	-	Site Master File
WHO	-	World Health Organization



2. GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labeling.
Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.
Site master File: is a document containing specific information about the activities undertaken in the pharmaceutical manufacturing site and is usually prepared by the manufacturer.

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

3. INTRODUCTION

3.1 The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical

manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

3.2 When submitted to a regulatory authority, the Site Master File should provide clear information on the manufacturer's GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

3.3 A Site Master File should contain adequate information but, as far as possible, not exceed 25 pages plus appendices on A4 paper sheets. Simple plans outline drawings or schematic layouts are preferred instead of narratives. The Site Master File, including appendices, should be readable when printed on A4 paper sheets.

3.4 The Site Master File should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The Site Master File should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each Appendix can have an individual effective date, allowing for independent updating.



4. SCOPE

These guidelines apply for all kinds of manufacturing operations such as production, packaging and labelling, testing, relabeling and repackaging of all types of medicinal products. The outlines of this guide could also be used in the preparation of a Site Master File or corresponding document by manufacturers of Active Pharmaceutical Ingredients.

5. LAY OUT OF THE SITE MASTER FILE:

5.1 Front Page:

Name and address of the applicant, Document number, Effective date, A bird view of the manufacturing site (photo), Date, Stamped

5.2 Table of contents

5.3 Approval page

Signed and dated by person(s) as prescribed by the Quality Management System

6. CONTENT OF SITE MASTER FILE

The Site Master File should include the following:

6.1 GENERAL INFORMATION

- 6.1.1 Contact information on the manufacturer
 - 6.1.1.1 Brief information on the firm (including name and address), relation to other sites and, in particular any information relevant

to understanding the manufacturing operations.

- 6.1.1.2 Name and physical address of the site, including GPS details, DUNS number (if available) telephone, fax, 24-hour telephone numbers
- 6.1.1.3 Name, phone number and e-mail for the contact person on the site
- 6.1.2 Authorized pharmaceutical manufacturing activities of the site
 - 6.1.2.1 Copy of the valid manufacturing authorization issued by the Local Drug Regulatory Authority should be provided in annex 1. If the local Drug Regulatory Authority does not issue manufacturing authorizations, the reason should be stated.
 - 6.1.2.2 A copy of current GMP certificate issued by the local regulatory authority should be provided in annex 2
 - 6.1.2.3 Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
 - 6.1.2.4 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site).
 - 6.1.2.5 Number of employees engaged in production, quality control, storage, and distribution.



6.1.2.6 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.

6.1.2.7 List of GMP inspections of the site within the last 3 years; including dates and name/country of the Competent Authority having performed the inspection.

6.1.3 Any other manufacturing activities carried out on the site.

6.1.3.1 Description of non-pharmaceutical activities on site, if any

6.2 QUALITY MANAGEMENT

6.2.1 The quality management system of the manufacturer

6.2.1.1 Brief description of the quality management systems run by the company and reference to the standards used.

6.2.1.2 Responsibilities related to the maintaining of the quality system including senior management

6.2.1.3 Information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies.

6.2.2 Release procedure of finished products

6.2.2.1 Detailed description of qualification (education and work experience) of the authorized person(s) responsible for batch certification and releasing procedures;

6.2.2.2 General description of batch certification and releasing procedure;

6.2.2.3 Role of authorized person in quarantine and release of finished products and in assessment of compliance with the marketing authorization;

6.2.2.4 The arrangements between authorized persons when several authorized persons are involved

6.2.2.5 Statement on the control strategies employed to release the different types of products e.g. process analytical technology (PAT) and/or real-time release or parametric release

6.3 MANAGEMENT OF SUPPLIERS AND CONTRACTORS

The Site Master File should provide information on management of suppliers and contractors as indicated below.

6.3.1 A brief summary of the establishment/knowledge of supply chain and the external audit programme;

6.3.2 A brief description of the qualification system of contractors,

6.3.3 Manufacturers of APIs and other critical materials suppliers;

6.3.4 Measures adopted where substandard/spurious/falsely-labelled/falsified/counterfeit medical products, bulk products, APIs or excipients are suspected or identified;



- 6.3.5 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- 6.3.6 List of contract manufacturers and laboratories including the addresses and contact information and flow-charts of supply chains for outsourced manufacturing and QC activities, e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw materials, etc., should be presented in annex 3
- 6.3.7 Description of the way in which the GMP compliance of the contract acceptor is assessed.
- 6.4 PRODUCT QUALITY REVIEWS**
- 6.4.2 Brief description of methodologies used.
- 6.5 PERSONNEL**
- 6.5.1 Organization chart showing the arrangements for quality assurance, quality control and production should be provided in Annex 4
- 6.5.2 QUALIFICATIONS, EXPERIENCE, AND RESPONSIBILITIES OF TECHNICAL PERSONNEL SHOULD BE INCLUDED AS ANNEX 5.
- 6.5.3 Outline of arrangements for basic and in-service training and how records are maintained.
- 6.5.4 Health requirements for personnel engaged in production.
- 6.5.5 Personnel hygiene requirements, including clothing.
- 6.6 PREMISES AND EQUIPMENT**
- 6.6.1 PREMISES**
- 6.6.1.1 Simple plan or description of manufacturing areas with indication of scale. Architectural or engineering drawings not required. Plant lay out should be attached in annex 6.
- 6.6.1.2 Nature of construction and finishes
- 6.6.1.3 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.
- 6.6.1.4 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned. Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%). Schematic diagrams should be added in annex 7.
- 6.6.1.5 Brief description of water systems with schematic drawings of the systems, including sanitation should be submitted. Quality references of water produced should be stated. Schematic diagrams should be added in annex 8.



6.6.1.6 Brief description of planned preventive maintenance programmes for premises and of the recording system.

6.6.1.7 Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc. Schematic diagrams should be added in annex 9.

6.6.1.8 Availability of written specifications and procedures for cleaning manufacturing areas

6.6.2 EQUIPMENT

6.6.2.1 Brief description of major equipment used in production and control laboratories together with the model, type and identification number. The list of equipment is should be provided in annex 10

6.6.2.2 Brief description of the procedures used for cleaning major equipment.

6.6.2.3 Brief description of planned preventive maintenance programmes for equipment and of the recording system.

6.6.2.4 Brief description of the company's Qualification and calibration policy, including the recording system. Reference should be made to the Validation master plan.

6.7 DOCUMENTATION

6.7.1 Arrangements for the preparation, revision, distribution and archiving of necessary documentation for manufacture should be stated.

6.7.2 Brief description of the validation master plan

6.7.3 Brief description of the change control procedure

9.7.4 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

6.8 PRODUCTION

6.8.1 TYPE OF PRODUCTS

6.8.1.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters. Reference to annex 11 should be made.

6.8.1.2 Policy for reprocessing or reworking should be stated.

6.8.1.3 Production capacities for the various dosage forms should be provided

6.8.2 PROCESS VALIDATION

6.8.2.1 Brief description of general policy for process validation. Reference should be made to the Validation master plan.

6.8.2.2 Arrangements for computerized systems validation

6.8.3 MATERIAL MANAGEMENT AND WAREHOUSING

6.8.3.1 Arrangements for the handling of starting materials, packaging materials, and bulk and finished



products, including sampling, quarantine, release, and storage.

- 6.8.3.2 Arrangements for the handling of rejected materials and products.

6.9 QUALITY CONTROL

- 6.9.1 Brief description of the quality control system: and the quality control department activities and procedures for the release of finished products should be stated.

- 6.9.2 Brief description of general Validation policy

6.10 DISTRIBUTION, COMPLAINTS, PRODUCTS DEFECT AND RECALL

- 6.10.1 Arrangements and recording system for distribution.
- 6.10.2 Arrangements for the handling of complaints and product recalls.
- 6.10.3 Arrangements for handling returned goods

6.11 SELF-INSPECTION

- 6.11.1 Short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

6.12 SHELF LIFE / STABILITY DETERMINATION PROGRAM

- 6.12.1 General policy for the determination of the shelf-life and stability of products manufactured at the site.

7. REFERENCES:

- 7.1. Annex 14-WHO guidelines for drafting a site master file (2011)
- 7.2. Explanatory Notes on the preparation of a Site Master File- Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, European Commission Enterprise Directorate-General
- 7.3. PIC/S Explanatory notes on the preparation of a Site Master File PE-008-4, (2011)

8.0 REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	September 2013	EAC TWG GMP Members	All	First approved version to be issued	REF: EAC/CM...../DECISION-----/dd/mm/yy



PART FOUR:
GUIDELINES ON
TRAINING AND QUALIFICATIONS



ABBREVIATIONS AND ACRONYMS

API	-	Active Pharmaceutical Ingredient
BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
EMA	-	European Pharmaceutical products Agency
EU	-	European Union
FEAPM	-	Federation of East African Pharmaceutical Manufacturers Harmonization
FPP	-	Finished Pharmaceutical Product
GCP	-	Good Clinical Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	-	Marketing Authorization
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
PIC/S	-	Pharmaceutical Inspection Convention Scheme
TWG	-	Technical Working Group
WHO	-	World Health Organization
QA	-	Quality Assurance
HVAC	-	Heating Ventilation and Air Conditioning
QC	-	Quality Control
QRM	-	Quality Risk Management
SOP	-	Standard Operating Procedure



1. GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

GMP Inspector means a GMP Inspector is an officer appointed by the NMRA of Partner states in accordance with national regulations and the provisions of the NMRA to conduct an inspection or assessment in order to verify GMP compliance of a manufacturing site on behalf of the NMRA.

Lead GMP inspector is a Senior GMP Inspector who is charged with the responsibility for leading a GMP inspection team to undertake inspection of a specified pharmaceutical manufacturing site(s).

Re-qualification implies validation of the GMP inspector after 24 months absence from conducting GMP inspections to ensure the officer possesses the knowledge and skills to carry out GMP inspections

Senior GMP inspector is an officer who by virtue of experience and competence is appointed as such to conduct GMP inspections and train junior officers in inspections after evaluation by the NMRA as by the criteria outlined in the assessment form.

Specialized GMP inspector is a GMP inspector who possesses specialized knowledge and experience in conducting GMP inspections for specialized areas e.g Microbiology, HVAC, Biologicals, API



2. INTRODUCTION

EAC NMRAs have a policy to conduct GMP inspections of all local and foreign sites at which medicines used in each member states are manufactured. This is to ensure adherence by manufacturers to all licensing provisions and specifically to GMP.

The main objective of GMP is to control and enforce general standards of production and to provide authorization for the manufacture of specific pharmaceutical products.

Specifically GMP inspection involves a sequential examination of production and control activities on the basis of the GMP guidelines issued by EAC NMRAs. In addition requires verification that production and quality control procedures employed in the manufacture of specific products are performed correctly and that they accord with data supplied in the relevant licensing applications.

Taking into account the paramount importance of the management of inspection services, this guidance establishes some requirements concerning experience, training, assessment and qualifications of GMP inspectors.

Objectivity and professional integrity, competence in technical matters and inspection skills should be the main features of inspectors.

Inspectors should be well trained in all the relevant topics concerning Quality Assurance management, manufacturing processes, control and distribution of medical products (including investigational medical products) and in the way of conducting an inspection (inspection methodology).

Inspectors should have previous training and practical experience in the manufacture and/or quality control of pharmaceutical products. Graduate pharmacists and chemists or scientists with an industrial background in pharmaceutical production, would qualify for consideration.

The guideline provides information on minimal requirements. They cover inspection of the production and control of final dosage forms of pharmaceutical products destined for human use and of drug substances (active pharmaceutical ingredients or bulk drug substances) employed in their manufacture. Inspection and licensing of pharmaceutical manufacturing facilities on the basis of compliance with GMP are a vital element of drug control.



SCOPE

This guideline applies to the training, assessment and qualifications required for an inspector who shall conduct an inspection to verify compliance with GMP for the EAC NMRAs.

3. GENERAL REQUIREMENTS

EAC NMRAs should appoint inspectors to inspect the local and foreign manufacturing sites at which medicines and medical products used in EAC member states are manufactured. There should be sufficient resources at all levels to meet, effectively and efficiently, the EAC NMRAs requirements of verifying compliance with GMP of medicinal products.

The inspectors shall be officials of or appointed by EAC NMRAs in accordance with the current Personnel Manual for each member state and shall follow EAC guidelines on GMP and the EAC standard operating procedures while preparing for, conducting and reporting on a GMP inspection.

All the inspectors should be competent to carry out their assigned duties and receive appropriate training. Since the number of inspectors allocated to a particular inspection is limited by economic and other considerations, each inspector should have all the basic qualifications and experience necessary to conduct an inspection independently.

Moreover, EAC NMRAs shall use the report on observations on all areas of the facility within the scope of the inspection to make a judgment on the status of the plant. Thus each inspector must be able to assess each section

of target inspection. However, when needed, teams of inspectors may be nominated comprising with appropriate qualifications and experience to collectively fulfill the requirements necessary for conducting the inspection.

The inspectors should be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of GMP-inspections according to EAC and national laws or international agreements.

EAC NMRAs and EAC Secretariat should put in place sufficient resources to ensure availability of competent inspectors to match the types and numbers of factories/products and frequency of inspection. The possibility of having part-time inspectors with specialist knowledge as part of inspection teams should also be considered.

The training of inspectors should regularly be assessed within requirements of the applicable quality system of the Inspectorate and appropriate action taken by EAC NMRA to maintain and improve inspection skills.

Information on the relevant experience, training and qualifications of individual inspectors must be documented and maintained by the Head of GMP Inspectorate in each NMRA or his/her designated representative. These records must be kept up-to-date.

4. QUALITIES OF A GMP INSPECTOR

The personal skills of an inspector are important in helping to achieve the objectives of the inspections.

During an inspection the inspector should help



in creating an open atmosphere. Inspectors need to remain objective during the inspection and in this context should answer questions or provide clarification but avoid entering into the role of a consultant.

The inspector should have a high personal integrity, maturity, honesty, be open-minded, understanding of complexity, possess sound judgment, assertiveness, analytical skills and tenacity and have the ability to perceive situations in a realistic way.

The inspector should have demonstrated competence in clearly and fluently expressing concepts and ideas orally and in writing in English and/or other languages defined by the EAC NMRA.

The inspector should also possess the following attributes:

- awareness of the probable methods of using forged or false documents for transactions in pharmaceutical preparations and skill in determining the genuineness of documents presented for examination
- responsible conduct which commands respect
- willingness to accept challenges
- ability to assess facts quickly and take rational and sound decisions without delay
- ability to assess character and honesty of persons being interviewed
- commitment to hard work and
- commitment to work for long hours

5. EDUCATION AND TRAINING

The inspector should have knowledge of the national and EAC legislation as well as systems for applications for marketing and control of marketed medicines.

The inspectors should have undergone training to the extent necessary to ensure their competence in skills required for planning, carrying out and reporting inspections. The training and experience should be documented individually and evaluated within the requirements of the applicable quality system of the GMP Inspectorate of the EAC NMRAs.

7.1 QUALIFICATION OF A GMP INSPECTOR

GMP Inspectors should normally be pharmacists preferably with exposure or working experience in the pharmaceutical industry. Where persons other than pharmacists are to be employed as GMP inspectors, they should be adequately experienced in drug control affairs and suitably trained in GMP inspectorate functions.

Moreover, in order to be appointed a GMP inspector by the respective NMRAs, the candidate should demonstrate their knowledge and skills in the relevant pharmaceutical field, including:

- Good Manufacturing Practice (Basic principles and annexes)
- Pharmaceutical technology
- Microbiology, process and ventilation engineering, analytical instrumentation, computer systems,



process validation, the statistical aspects of quality control

- Interrelation of inspection, sampling and analysis, licensing
- Marketing and manufacturing authorization systems and their relationships
- Auditing/inspection techniques
- Training in inspection technique, acquired by attending relevant courses and/or by accompanying and/or be guided by qualified GMP inspectors during inspections
- Training in administration procedures required for managing an inspection, such as planning, organizing, communicating or providing feed back to inspectee
- Training in evaluation of findings and reporting
- Distribution of medicinal products
- National and international medicine legislations
- Communication skills, oral and written
- Organization of the national medicine regulatory authority
- The general principles of Quality Management Systems (ISO 9000:2000, etc)
- Knowledge of the Quality systems of the EAC NMRA GMP Inspectorate

- Knowledge of and training in working according to relevant EAC NMRA's SOPs for inspections
- Structure and principles of operation of commercial organizations
- Judiciary procedures

7.2 IN-SERVICE TRAINING

After recruitment and in addition to their basic training, new inspectors should be trained by senior inspectors. The theory of inspection should be explained and the practice should be shown in the field, so that concrete examples of the meaning and of the goals of inspections are given and can be discussed. New inspectors should participate, but only as observers, in on the spot inspections carried out during their initial training.

Training of inspectors should be a combination of theoretical and practical training. It should cover both technical and non-technical aspects.

Prior to assuming responsibility for performing GMP inspections, the new inspector should have gained experience by participation as a team member in inspections led by senior inspectors. Preferably, the inspector should start with national GMP inspections as a member of a team and then deal progressively with more complex GMP inspections to be able to act as a team leader and/or reporting inspector in international inspections.

This should consist of six phases:

1. **Initially** the trainee is trained in the basic principles of GMP and good inspection techniques.



2. In addition, the trainee inspector should have assessed at least ten (10) dossiers prior to qualification as a GMP inspector
3. The trainee inspector would participate in a GMP inspection with experienced inspector as an observer in at least three inspections.
4. **Secondly**, the trainee inspector would participate in inspections as a junior member of the team (at least six inspections).
5. **Thirdly**, the trainee inspector would participate in inspections as a co-inspector under supervision of a qualified lead inspector (at least three inspections). After assessment and satisfactory performance, the trainee qualifies as a GMP inspector.
6. **Finally**, the GMP inspector would participate in inspections as a co-inspector in at least twenty inspections at national, regional or international level taking into consideration of different dosage forms and expertise acquired to become a lead GMP inspector after assessment of satisfactory performance.

At all stages, the performance of the trainee should be assessed according to the assessment form in annex 1 attached.

This should be recorded within the requirements of the applicable quality system of the EAC NMRA GMP Inspectorates Besides this and where needed, training courses in auditing techniques and

communication, reporting, language, legal matters and management should be organized by EAC NMRA GMP Inspectorates.

7.3 CONTINUOUS TRAINING

Considering the dynamic nature of manufacturing technologies, the ever more frequent utilization of automatic and computerized systems both in production and quality control of medicinal products, inspectors should also receive continuous training. This could be reached through their participation in courses, seminars, scientific meetings and conferences organized by either EAC NMRA GMP Inspectorates or by national, regional or international scientific organizations.

When appropriate, joint inspections or training visits with other inspectors of the EAC NMRA or other DRAs may be a useful training method.

GMP Training in form of courses, symposiums, conferences, or any other mode the NMRA deem suitable) should be arranged by EAC NMRA on annual basis.

8. MANAGEMENT CAPABILITIES

The inspector should through suitable means demonstrate their knowledge and capability of using the necessary management skills required in execution of an inspection, i.e. planning, announcing, conducting and reporting an inspection.



9. REPORT WRITING

The inspector should document and demonstrate their capacity to write inspection reports according to EAC NMRA requirements as prescribed in the EAC Model Procedure for Preparing and Reviewing of GMP Inspection Reports (EAC/TF-MED/GMP/FD/SOP/N6R0). An inspection should be regarded as an opportunity to assist and motivate a manufacturer to comply with GMP and to correct any specific deficiencies. It should not be limited to compilation of an inventory of faults, irregularities, and discrepancies.

Negative observations (non-compliance with GMP requirements) should distinguish between whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

10. MAINTENANCE OF COMPETENCE AND DISQUALIFICATION

Inspectors should have their performance and qualifications periodically reviewed within the requirements of the quality system of the EAC NMRA GMP Inspectorates.

Their competence should be maintained and updated by practical experience and participating in courses, seminars, scientific meetings, conferences and review of relevant publications.

This should be documented and its effectiveness assessed, In quality assurance

activities, within the requirements of the applicable quality system of the EAC NMRA GMP Inspectorates:

- Ensuring that the knowledge of GMP, quality systems standards and requirements is current,
- Ensuring that the knowledge of inspection procedures and methods is current,

EAC NMRAs should arrange annual training for all GMP inspectors to either refresh the knowledge of GMP inspection among the inspectors.

Inspectors should be assessed based on the number of GMP inspections performed, trainings undertaken, adherence to the Code of Conducts for GMP inspectors and outcome thereof on annual basis and this will form a basis for considering further assignment of GMP inspection.

GMP inspectors should conduct at least one GMP inspection every year in order to maintain their status as GMP inspector.

A GMP inspector who has not been performing GMP inspection for more than twenty four months, should be re-qualified before one is allowed to conduct further GMP inspections. The inspector to be re-qualified should participate in GMP inspection as a team member.

Disqualification of a GMP inspector shall follow the laid down procedure regarding disciplinary action in accordance with respective NMRAs human resource policy and Code of Conduct.

A GMP inspector shall be assessed by at least three senior GMP inspectors.



11. INTERNATIONAL AND REGIONAL COLLABORATION

In order to promote international harmonization in the interpretation of the principles and compliance, the GMP inspection program management should facilitate training activities, including on the job training, at national, regional and international levels.

Consultations with the staff of the other GMP inspectorates and joint inspection or training visits may be useful and should be encouraged.

The management should also facilitate the exchange of information and practical experience gained by inspectors in the fields of GMP, especially on those parts that are closely related to GCP, e.g. laboratory facilities, computerized data recording and analyses and requirements in relation to medicinal products for investigational use.

12. REFERENCES

European Medicines Agency (EMA) Guideline on Training and qualifications of GMP inspectors, 2008

13. REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	17th April 2014	EAC TWG GMP Members	All	First approved version to be issued	REF: EAC/SC/ DECISION---- /17TH APRIL 2014



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