TMDA/DMC/MCIE/G/014
REV.1

UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES FOR PRODUCTION OF EXTEMPORANEOUS FORMULATIONS AND HOSPITAL BASED STERILE PREPARATIONS

Second Edition

April 2022

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ABBREVIATIONS

AC	-	Air conditioning
API	-	Active Pharmaceutical Ingredient
CFU	-	Colony Forming Units
DNA	-	Deoxyribonucleic acid
DQ	-	Design Qualification
EED	-	Evangelical Lutheran Church in Germany
ELCT-IUP	-	Evangelical Lutheran Church of Tanzania-Infusion Unit Project
GCP	-	Good Clinical Practice
GLP	-	Good Laboratory Practice
cGMP	-	Current Good Manufacturing Practice
HEPA	-	High Efficiency Particulate Air
HVAC	-	Heating Ventilation and Air-Conditioning
INN	-	International Non-Proprietary name
IQ	-	Installation Qualification
ISO	-	International Standard for Standardization
KCMC	-	Kilimanjaro Christian Medical Centre
LAL	-	Limulus Amoebocyte Lysate
MSDS	-	Materials Safety Data Sheets
OQ	-	Operational Qualification
QA	-	Quality Assurance
QC	-	Quality Control
PIC/S	-	Pharmaceutical Inspection Convention Scheme
PQ	-	Performance Qualification
PV	-	Process Validation
SOP	-	Standard Operating Procedures
SS316L	-	Stainless Steel 316L
TMDA	-	Tanzania Medicines and Medical Devices Authority
TPH	-	Tanzania Pharmaceutical Handbook
TSE	-	Transmissible Spongiform Encephalopathy
VMP	-	Validation Master Plan
WHO	-	World Health Organization
WPU	-	Water for Pharmaceutical Use

ACKNOWLEDGEMENTS

I wish to take this opportunity on behalf of TMDA to thank all who participated in the review of these Guidelines. Special thanks should go to the following TMDA staff: Mr. Emmanuel Alphonce, Ms. Siya Augustine, Mr. Paul Sonda, Ms. Estella Meena, Dr. Daniel Fussi, Dr. Agness Yongolo and Mr. Maganga Bundala.

Special thanks are also extended to TMDA Management Team for constructive inputs and endorsement of the guidance document.

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FOREWORD

The Tanzania Medicines and Medical Devices Authority (TMDA) was established under the Tanzania Medicines and Medical Devices Act, Cap. 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of medicines, medical devices and In- vitro diagnostics. The Authority has a legal responsibility of ensuring that all regulated products manufactured or compounded and used in the country meet the prescribed standards for the intended use.

In order to streamline and effectively control compounding of medicinal products in hospitals and pharmacies, these Guidelines for Production of Extemporaneous and Hospital Based Sterile Preparations was first crafted in July, 2017.

This is the Second revision of the Guidelines and its purpose is to assist pharmacists in discharging their legal and professional obligations to patients in the area of extemporaneous dispensing. This guidance will help to assure the safe and appropriate preparation and supply of extemporaneously prepared medicinal products to patients, where the supply of such products is necessary.

Extemporaneous and hospital based sterile preparations are critical for patients whose clinical needs cannot be met by registered medicinal products. The guidelines outline the principles and application of the concepts of Good Manufacturing Practice (GMP) requirements for premises, equipment, personnel, storage, quality management system, quality control, compounding processes as well as documentation.

The guidelines also provide for the current technical guidance on minimal requirements for production of extemporaneous and hospital based sterile preparations. Its aim is to provide guidance to pharmacists to ensure product quality, safety and efficacy. These guidelines should be used together with other TMDA guidelines which apply to the importation, storage and distribution of all medicines including compounded medicines. The guidelines can also be used as a training tool for personnel compounding medicines, GMP auditors and training institutions.

It is expected that the document will be used and enable consistent and uniform procedures for the production of extemporaneous and hospital based sterile preparations so that they can consistently meet safety and quality standards. Nevertheless we welcome new ideas, opinions and suggestions in this context that will assist in improvement of the guidelines.

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Director General
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BACKGROUND

Extemporaneous preparations are small scale compounding products prepared at the approved facility by qualified personnel for individual patient use. Normally these preparations are prepared when registered dosage forms of a therapeutically equivalent product is not available.

On the other hand, an extemporaneously prepared medicinal product refers to the process by which a pharmacist, using traditional compounding techniques, produces a medicinal product to meet the special needs of a patient, or group of patients.

Extemporaneously prepared medicines are usually not registered and are not subject to regulatory reviews. Therefore, neither prescribers nor pharmacists can make the same assumptions of quality, safety and efficacy about these products as they do for registered medicines.

These guidelines have therefore been prepared to regulate the practice and provide minimum requirements for hospitals and pharmacies engaging in extemporaneous preparations.

The extemporaneous preparation of medicinal products is a recognised part of a pharmacist's skill set. However, it must also be recognised that where an extemporaneous product is prepared by a pharmacist it has not undergone an evaluation of its quality, safety and efficacy by TMDA as is the case for authorised products.

Accordingly, the responsibility for assuring the quality and safety of these extemporaneously prepared products, with a view to the achievement of their therapeutic purpose, rests with the pharmacist under whose authority they are prepared. In the discharge of this responsibility, the added value which these products contribute to the care of the patient must also be taken into account.

The pharmacist should always be satisfied that he or she has the necessary facilities and competence to undertake the extemporaneous dispensing and is thereby in a position to supply a product of appropriate quality and safety.

Pharmacists must always be satisfied that any product they prepare is safe and fit for purpose at the time of preparation, at the time of supply to the patient and throughout the projected shelf life.

It should be noted that hospitals or pharmacies are not allowed to wholesale extemporaneously prepared medicines to other pharmacies or hospitals. Due to the lack of age-appropriate products, extemporaneous dispensing plays an important part in meeting the needs of pediatric patients.

On the other hand, the guideline also highlights minimum requirements for production of sterile preparations in hospital set-ups. Production of large-volume parenterals can be done in large scale (industrially), as well as small scale in hospital pharmacy, for consumption locally. But whether, it is carried out in large scale at industrial level or in small scale within hospital settings, the same basic principles of Good Manufacturing Practices (GMP) shall apply.

Moreover, production of intravenous fluids (IV fluids) involves operations of purchase of materials, production processes, quality control, storage and distribution of finished products of highest quality standards. Such operations need to be carried out according to GMP that forms an important part of a comprehensive system of quality assurance. Adherence to prescribed guidelines that takes into account the basic elements of GMP ensures that locally produced IV fluids are prepared to meet quality standards required for their intended use.

The small-scale pharmaceutical production or compounding is economically feasible for certain medicines including IV fluids for consumption locally by needy patients and with minimal quality control. This is in contrast to large scale pharmaceutical production by commercial companies for distribution in a large geographical area, but with guaranteed and validated product quality. However, the same principles of GMP can be adapted and applied to any local situation with use of appropriate intermediate technology and simplified techniques to assure the same product quality.

Basically, a hospital pharmacy must not undertake local production of sterile preparations unless it can guarantee a sufficient and reliable source of purified water, supply of quality raw and primary packaging materials, well-designed premises, appropriate equipment and skillfully trained personnel to carry out required operations/processes to assure a product of sufficient and standard quality.

When all these factors are present and basic quality control is assured, the pharmacy is capable of producing these preparations and contributes significantly to the health care of patients in hospitals.

For many years in Tanzania there was scarcity of medicines in hospitals caused by financial constraints for importation of life saving infusions. Coupled with difficulties in transportation due to poor infrastructure in the past, many hospitals engaged in compounding medicines including infusions in their hospital pharmacy for their patients. The produced infusions were in very small quantities due to use of inappropriate and high energy consuming technology.

To address the aforementioned shortcomings in hospital production of infusions in 1977, Georg Kamm, a German Anaesthetist who was working at Machame Lutheran Hospital, approached a German Pharmacist for technical assistance in advising an appropriate technology. They established the first hospital-based infusion production unit using Reverse Osmosis machine for water purification which produces enough purified water at a shorter time and consumes low energy.

After a short period, other hospitals learnt from the success of Machame Hospital and started requesting for technical assistance to establish such units in their own hospitals. This was the birth of Evangelical Lutheran Church (ELCT) - Infusion Units Project (IUP).

The project has been supported by the Evangelical Lutheran Church in Germany (EED) and Mission One World (Bavarian Lutheran Church). In 1986 the long-term cooperation with the Medical Mission Institute, Wuerzburg in Germany started with regular consultancies focusing on research and advice on appropriate technology and standards, followed by cooperation with the German Institute for Medical Mission in Tuebingen.

In 1991, the base of the Infusion Project moved from Machame Hospital to its present location in Moshi Municipality within the Kilimanjaro Christian Medical Centre (KCMC) compound.

In 2004, ELCT transformed the project and established a registered trust under the church currently known as Saint Luke Foundation which took over the activities of the ELCT-IUP which later became the 'Infusion Units Program' as one of the programs among others which were established like Kilimanjaro School of Pharmacy.

The success of the Infusion Units Program from its establishment, anchored on the following philosophy:

a) Conducting and organizing tailor made training and retraining/refresher courses on hospital-based production of infusions.
b) Research on standardizing production equipment for ease of repair and maintenance.
c) Professional installation of the equipment and machines.
d) Conducting annual supportive supervision visits to hospitals and doing preventive maintenance and calibration/validation of equipment and assure in-process quality controls are adhered.
e) Pre-qualifying and selecting reliable suppliers and procurement of production supplies.

In 1988, the first edition of Tanzania Pharmaceutical Handbook (TPH) which contained a number of formula for compounding was prepared by B. Liebsch (Mrs), D. S. Nyamageni, S. S. Senya and K. F. Steinhausen and started to be used for teaching Pharmacy students. TPH was revised in 2011 and continue to be used for teaching pharmaceutical practices.

INTRODUCTION

These guidelines outline specific points for the production of extemporaneous and hospital-based sterile preparations or large and small volume parenterals produced at hospital settings to minimize risks of particulate, microbial and pyrogens contamination. The requirements described in these guidelines should be considered as minimum and shall be binding to all health facilities involved in extemporaneous and hospital based sterile preparations after being inspected and approved by TMDA.

These guidelines are not meant to replace other legal controls, but rather to supplement them with the aim of minimizing risks such as contamination and mix ups and ensure product quality, safety and efficacy. To achieve this, there must be a comprehensively designed and correctly implemented system of quality assurance incorporating basic GMP and quality control.

The pharmacist responsible for preparing or procuring an extemporaneously prepared medicine and sterile preparations should therefore take responsibility for ensuring that the medicine is of suitable quality and is safe and efficacious. Failure to do so puts both the pharmacist and organization at risk in terms of both civil and negligence liability. The pharmacist should also ensure that the prescriber is aware of the unregistered status of the medicine and any associated risks with its use.

Extemporaneous preparation should therefore only be considered when an equivalent registered product is unavailable or is unsuitable for use and if the use can be clearly justified clinically and pharmaceutically. Consideration should be given to all alternatives before choosing this option.

However, it is recognized that some patients may have special clinical needs that cannot be met by registered medicinal products or by a viable alternative option. In these circumstances it would be inappropriate to curtail the patient's treatment, as this would have a detrimental effect on their condition. Whenever carrying out a risk assessment, the risks of not treating the patient should also be considered and be at the forefront of the decision-making process.

The use of a registered medicine from the same therapeutic classification should be considered first than the use of an extemporaneously prepared medicine which has limited data to support its formulation and stability. However, the decision to switch to a different medicine should also take into account the condition of the patient and the relative toxicity of the medicine.

For example, if a patient is stabilized on a medicine with a narrow therapeutic index, it may have a more detrimental impact on the patient's well-being to switch to a different, but therapeutically equivalent medicine than using a medicine that has been extemporaneously prepared against a validated formulation. The use of an alternative route of administration, for example use of the rectal rather than the oral route could also be considered if an appropriate formulation is available. Extemporaneous preparations are mostly required at times in pediatrics, elderly care, dermatology and emergency medicine.

All activities performed during extemporaneous compounding should be appropriately documented as per respective SOP's.

RISK MANAGEMENT

The extemporaneous preparation of medicines is associated with a number of potential risks to patients, healthcare staff and their organization. All these need to be carefully considered in determining the best treatment option; they then need to be minimized when the use of this category of medicine is necessary.

A risk assessment should be performed before making a decision to extemporaneously prepare a medicine. This process should be underpinned with a procedure in place and records of risk assessments maintained on file.

This section gives guidance on the risks associated with extemporaneous preparations, the assessment and management of these risks and alternative options.

Legal background and organizational risks

Extemporaneously prepared medicines are unregistered medicines and are not subject to TMDA registration requirements. Therefore, neither prescribers nor pharmacists can make the same assumptions of quality, safety and efficacy about these products as they do for registered medicines.

Alternatives to extemporaneous preparations

There are a number of alternative options that should be carefully considered as part of a patient-specific clinical risk assessment before opting for extemporaneous preparations. Some of the options include;

- Therapeutic substitution
- Use of unregistered imported product on special requests
- Use of soluble or dispersible tablets instead of extemporaneous prepared liquid
- Cutting tablets
- Use of a preparation intended for a different route of administration

Risks associated with extemporaneous preparation

- Formulation failure
- Microbial contamination
- Calculation errors
- Validity of the formulation
- Toxicity of some starting materials (Inappropriate starting materials)
- Labelling errors
- Poor patient acceptability of the finished product
- Unknown stability and shelf life of the finished product
- Health and safety of staff members involved in the preparation of the product

Potential causes of calculation errors can include:

- Unclear instructions from the prescriber
- Conversion between units e.g. milligrams to micrograms
- Confusion between a medicine in its free base and its salt form
- Misplaced decimal points
- Errors whilst carrying out dilutions

A lack of knowledge and familiarity with traditional terminology e.g. double strength chloroform water, single strength chloroform water and concentrated chloroform water.

Record Keeping

A clear record in respect of each extemporaneously prepared product must be made and kept to ensure full traceability of the ingredients, formulae and method used, and the names of all pharmacists and staff members involved. The information to be recorded should be clearly stipulated in a standard written procedure. A recall procedure should be in place in case a defect or error is identified and the product has to be returned to the pharmacy.

At a minimum, the following must be recorded each time a medicine is extemporaneously prepared for supply to a patient (in the exceptional circumstances of batch manufacture some information may not be relevant):

- Patient's name
- Patient's address and contact details
- Name and address of the patient's prescriber
- Other prescription details as applicable e.g. date, type of prescription
- Date of preparation
- Formulation used, and source e.g. pharmacopoeia formula, if applicable
- Calculations and workings
- Details of each preparation step
- Name, strength, grade (Pharmaceutical material) and quantity of each ingredient or material used
- Source of starting ingredients or materials i.e. manufacturer and wholesaler
- Batch number and expiry date of each ingredient or material used
- Storage conditions and expiry date of the finished product
- Identity of the staff member who carried out the preparation process and the identity of the pharmacist under whose supervision the process was carried out
- Results of any quality control tests carried out
- A record sheet (can also be called a work sheet) should be made for each individual preparation and a duplicate dispensing label affixed thereon. This record should be maintained for at least two years on the pharmacy premises and be available for inspection. The record sheet should facilitate a checking mechanism at each stage of the procedure and provide a clear audit trail of the ingredients used and process followed.

GLOSSARY OF TERMS

For the purpose of these guidelines, the following terms are defined as follows:

Act:

Means the Tanzania Medicines and Medical Devices Act, Cap 219

Airlock:

Means 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 use either by people or for goods and/or equipment.

Aseptic technique:

Is a set of specific procedures performed under carefully controlled conditions with the goal of minimizing contamination pathogens.

Authority:

Means Tanzania Medicines and Medical Devices Authority or its acronym TMDA.

Batch:

Means defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous.

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.

Contamination:

Means introduction of undesired impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting or intermediate material during production, sampling, packaging or repackaging, storage or transport.

Cross-contamination:

Means contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Documentation:

Means all written procedures, instructions and records involved in the manufacture and quality control of products.

Exempt medicinal products:

Means unauthorised medicinal products for individual patients under their direct responsibility prescribed in order to fulfil special needs of those patients.

Extemporaneous preparations:

Means preparations small scale compounding products prepared at the approved facility by qualified personnel for individual patient use.

Finished Product:

Means a finished dosage form that has undergone all stages of manufacturing operations including packaging in its final container and labelling.

Good Manufacturing Practice (GMP):

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 and as required by TMDA.

Hospital based sterile preparations:

Means large or small volume parenterals or eye preparations produced at hospital settings.

Infusion unit:

A designated building or premises where all operations involved in the preparation of hospital-based sterile preparations, from receipt of materials, through processing, packaging, sterilization, labelling to completion of the finished product, to storage and distribution to the respective hospital pharmacy is done.

Label:

Means any tag, brand mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any medicine, medical device or in- vitro diagnostic.

Large-volume parenterals:

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

Manufacture:

All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer:

Means a person or a firm that is engaged in the manufacture of products regulated by TMDA.

Packaging:

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging materials:

Any material, including printed material, employed in the packaging of a pharmaceutical, but 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.

Pharmacist:

Means a person who is registered as a pharmacist under the Pharmacy Act, 2002.

Pharmacy:

Includes a registered pharmacy department in a hospital, clinic or health centre or a community pharmacy.

Production:

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and re-labelling, to completion of the finished product.

Raw materials:

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

Standard Operating Procedure (SOP):

An authorized written procedure, giving instructions for performing operations Documented Standard Operation Procedures

PART I: GUIDELINES FOR EXTEMPORANEOUS COMPOUNDING

CHAPTER 1: PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of compounding and control of medicinal products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks.

General

1.1 A Pharmacist or Pharmaceutical Technician with sufficient training and/or experience shall be designated as responsible for compounding operations within the hospital.

1.2 Designated Pharmacist or Pharmaceutical Technician with adequate supervision may delegate some of the compounding activities to other healthcare professionals who have the knowledge and skills for preparation of medicinal products.

1.3 Designated Pharmacist or Pharmaceutical Technician should use their professional judgment when deciding whether they have the expertise to compound a specific product and should be aware of Good Manufacturing Practices.

1.4 Only one product shall be prepared at a time within the designated area to avoid mix-ups and/ or cross contamination.

Training

1.5 Personnel involved in compounding shall receive adequate orientation, suitable didactic and experimental training in compounding, proper gowning, gloving and cleaning procedures. They should be trained and evaluated for their competence through written and practical testing.

1.6 Annual training programs and evaluations should be available for all personnel to maintain expertise in compounding activities.

1.7 The designated pharmacist or pharmaceutical technician should be responsible for the training and evaluation of all staff involved in compounding activities including cleaning personnel.

Hygiene

1.8 Personnel involved in compounding should maintain high standards of personal hygiene and cleanliness.

1.9 Personnel with any health condition which may adversely affect the safety and quality of compounded products shall be assessed and exempted from responsibilities in the area, if necessary.

1.10 Written procedures detailing the minimum requirements for health and hygienic behaviour of individuals performing compounding activities should be addressed in a policy manual which shall include but not limited to: suitable dress (e.g. gowns,

masks, gloves, and footwear), hand hygiene and health conditions as well as open lesions.

CHAPTER 2: PREMISES

Principle

Premises for compounding must be located, designed, constructed, adapted and maintained to suit the compounding 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 mix-up, cross contamination, build-up of dust or dirt and in general, any adverse effect on the quality of compounded products.

General

2.1 Premises engaging in compounding shall have specifically designated area for orderly storing of equipment and materials to be used. The premises should be preferable not near areas with a lot of movements like patients and other personnel passing nearby.

2.2 Access to compounding area shall be restricted to authorized personnel.

2.3 The compounding section shall have the following design:

a) Walls tiled or oil painted
b) Floors covered with tiles, terrazzo or sealed cement finish
c) Windows of adequate size to provide sufficient light which can be closed during compounding, ideally the area should have air conditioning
d) Water tap and sink
e) Cupboard(s) to store equipment
f) Shelves for containers of ingredients and preparations
g) Benches or tables of plain wood with varnish, oil painted or Formica cover
h) A wall rack to dry equipment

2.4 The designated area shall be maintained in a clean and sanitary condition, permit effective cleaning of all surfaces and shall be in a good state of repair to minimize the potential for contamination of the product or addition of any extraneous material to the product.

2.5 The designated area for compounding shall be sufficiently ventilated to allow air circulation and provided with adequate lighting.

2.6 There should be a written and implemented sanitation program to include the cleaning requirements for the premises and equipment.

CHAPTER 3: 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 according to cGMP standards.

General

3.1 Equipment used for compounding should be in an area that permits it to function in accordance with its intended use. Equipment should be operated in a manner that prevents contamination.

3.2 The parts of equipment that come into contact with the product shall not be reactive, additive, absorptive to such an extent that it will affect the quality of the product and thus present any hazard, i.e. it shall be of glass, porcelain or stainless steel.

3.3 Equipment should be easily and routinely cleaned to minimize the potential for contamination and suitable for preparation of the desired compound.

3.4 Equipment should be kept clean, dry and protected from contamination during storage to prevent the addition of extraneous materials and status labels should be available.

3.5 There should be a written procedure for cleaning critical compounding equipment and procedure for re-cleaning before use.

3.6 Equipment used for measuring and weighing should be calibrated, if appropriate on regular scheduled basis and documentation showing proof of calibration and servicing should be maintained in the pharmacy records.

3.7 Consideration should also be given to the type of container used to supply the finished product, for example how it may affect the product's stability and use.

CHAPTER 4: MATERIALS

Principle

The main objective of compounding is to produce finished products for patients' use from a combination of materials (starting and packaging).
Materials include starting materials, solvents, process aids, reagents, packaging materials and labelling materials.

General

4.1 Raw materials shall be sourced from known suppliers in the country and when sourced from outside the country an import permit from TMDA should be available.

4.2 Raw materials shall be received, handled and stored in a manner to prevent contamination of products.

4.3 Raw materials used in compounding should be stored in adequately labelled containers in a clean, dry area and if required under proper refrigeration.

4.4 The quality and identity of all raw materials used in compounding should be verified using a certificate of analysis from a supplier or the label claims of commercially available products used in the compounding process.

4.5 Specifications should be of a pharmacopoeial or equivalent standard.

CHAPTER 5: COMPOUNDING PROCESS

Principle

Written procedure should be in place for each compounded product to ensure that the final product will meet the specifications of that product and have consistent results.

General

5.1 The designated pharmacist should gather sufficient information to make knowledgeable decisions regarding a formulation and process of compounding.

5.2 Formulations should be developed based on official publications. If no official publication is available, a formula should be developed using the pharmacist's professional knowledge and skills in pharmacology, chemistry and therapeutics and such formulation should be scientifically justifiable.

5.3 Designated pharmacist or pharmaceutical technician shall assume responsibility for the final products and carry out appropriate checks at critical steps in the process.

5.4 Master Formula.
The master formula should include:

a) The name of product
b) The dosage form of the product
c) The specifications and source of each raw materials used
d) The formulation of each batch stating weight and measures of each raw material and theoretical yield
e) The equipment required
f) A description of each step in the compounded process with special notation required (e.g. which steps or measurement must be verified by pharmacist or a second person)
g) The shelf life when applicable.
   The expiration date (shelf life) of the compounded product should base on the known stability of the molecule(s) compounded and shall not exceed the expiration date of the starting raw materials. Expiration periods should be derived using any or all of the following references:
   i. manufacturers' recommendation
   ii. pharmaceutical compendia
   iii. professional literature and
   iv. in-house stability and/or sterility studies
h) The storage requirement
i) The specific packaging requirements
j) A sample label
k) The quality control testing to be performed when applicable
l) The reference sources for the formula, stability data if available.

5.5 The steps to be followed before, during, and after compounding shall be grouped into five categories namely preparatory, compounding, final check, sign-off and clean up steps.

Preparatory

5.6 Designated pharmacist or pharmaceutical technician shall

a) Clean the compounding area and the equipment if necessary
b) Judge the suitability of the prescription in terms of its safety and intended use and the dose for the patient
c) Perform the calculations to determine the quantities of the ingredients needed
d) Select the proper equipment and making sure it is clean
e) Wear the proper attire and washing hands according to the respective written procedures
f) Assemble all the necessary materials and ingredients to compound and pack the prescription.

Compounding

5.7 Designated pharmacist or pharmaceutical technician shall compound the prescription according to the formulary record or the prescription, using techniques according to pharmaceutical knowledge and skills, strictly observing GMP procedures.

Final Check

5.8 Designated pharmacist or pharmaceutical technician shall check and ensure adequacy of mixing, clarity, odor, color, and pH.

5.9 Designated pharmacist or pharmaceutical technician shall enter the information in the compounding log and label the prescription.

Sign-Off

5.10 Signing and dating the prescription, affirming that all of the indicated procedures were carried out according to the prescribed standard procedures to ensure uniformity, identity, strength, quantity, and purity

Cleanup

5.11 Cleaning and storing all equipment.
5.12 Cleaning the compounding area.

CHAPTER 6: QUALITY CONTROL REQUIREMENTS

6.1 Pharmacist should ensure the quality of the ingredients by using materials of pharmaceutical grade or recognized pharmacopoeia standards with a valid batch number and expiry date etc.

6.2 The pharmacist responsible for preparing or procuring an extemporaneously prepared medicine should take responsibility for ensuring that the medicine is of suitable quality, and is safe and efficacious.

6.3 The extent of quality control applied to a product should be proportionate with the level of risk the finished product could pose to the patient and should be judged on a case by case basis.

6.4 Consideration should be given to the individual patient's age and condition, whether the product will be ingested or used topically, as well as the potency of and risk posed by the active substances and/or excipients.

6.5 Where it is not practical to carry out this testing (e.g. due to the batch size, urgency, etc.), other suitable methods (quality assurance and quality control measures) should be implemented to ensure that the appropriate quality is achieved.

6.6 At a minimum, starting materials and finished product should be examined visually before being used or supplied to a patient.

6.7 All raw materials used during extemporaneous preparations have to bear valid certificate of analysis from reputable source or supplier before they are used in the compounding area.

CHAPTER 7: DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system, and, as such, should be related to all aspects of cGMP standards. It aims to define the specifications for all materials and methods of compounding and control to ensure that all personnel concerned with manufacture know what to do, how to do and when to do it.

Documentation helps the Pharmacist to gather all the information necessary to decide whether or not to compound a particular product.

Documents must be free from errors and available in writing. The design and use of documents depend upon the Pharmacist.

Pharmacist should maintain supportive documents such as specifications, Certificate of Analysis or Conformity, material safety datasheet (MSDS) and Transmissible Spongiform Encephalopathy (TSE) statement to assess whether the product is of appropriate quality. National Formulary and other essential reference books should also be available.

General

7.1 Documents should be designed, prepared and reviewed timely.

7.2 Data may be recorded by electronic data-processing systems or by photographic or other reliable means.

7.3 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.

7.4 Documents should have unambiguous contents. They should be prepared according to written procedures and laid out in an orderly fashion which is easy to check. Reproduced documents should be clear and legible.

7.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent unintentional use of the superseded version.

7.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

7.7 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.

7.8 If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer.

7.9 Access to that computer should be restricted by passwords or other means.

PART II: GUIDELINES FOR PRODUCTION OF HOSPITAL BASED- STERILE PREPARATIONS

Principle

Like other pharmaceutical products, sterile preparations should be manufactured by sufficiently qualified pharmaceutical personnel. Proper training, skills and attitude of the workers during the manufacturing process will doubtlessly contribute to the quality of the final product far more than perfect and expensive equipment. The 'ideal' qualified personnel involved in the manufacture of sterile products should be:

a) Devoted to professional ethics, i.e. participating in providing good health services by giving her/his best to produce preparations of acceptable standards;
b) Equipped with basic understanding of pharmaceutical technology, microbiology and hygiene;
c) Aware of the hazards which can be caused by using products of poor standard;
d) Aware of the sources of contamination and at which time during the production process contamination may occur.

General

The manufacture of hospital based sterile preparations 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.

Manufacturing of hospital based sterile preparations should only involve products which can be terminally sterilized in their final container/pack.
Extra precautions should be taken for sterile preparations which actively support microbial growth such as Dextrose 5% and filling operations at slow speed or if the container has a wide neck.

Production of hospital-based sterile preparations should be conducted in a controlled environment (free from particulate and microbial contamination) so as to reduce contamination during preparation.

This guideline is not a standalone document hence it must be used concurrently with other available useful information such as contents available in part I of this document.

CHAPTER 1: PERSONNEL

1.1 Personnel engaged in the production of sterile preparations should be healthy to perform their assigned duties and they should undergo regular health examinations at least once every six months.

1.2 Personnel should be trained in the practices of personal hygiene and in particular they should be instructed to wash their hands before entering production areas.

1.3 Any personnel 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 raw materials, packaging materials, in-process materials, and finished products.

1.4 Personnel should report to their immediate supervisor any conditions (plant, equipment or personnel) that they consider may adversely affect the products.

1.5 Direct physical contact with the product should be avoided to ensure protection of the product from contamination. Personnel should wear protective and clean attire appropriate to the duties they perform.

Training

1.6 Personnel should be trained appropriately to their assigned duties and evidences should be available.

1.7 Personnel appointed to be involved in production of hospital-based sterile preparations should receive adequate training on hospital production of intravenous fluids from a recognized training institution.

1.8 Qualified pharmaceutical personnel (i.e. Pharmacists and Pharmaceutical Technicians) should provide daily routine supportive supervision on production of intravenous fluids within their respective hospital having such infusion unit.

1.9 Personnel engaged in cleaning the production area must also receive training on the special cleaning conditions in the area.

1.10 Visitors or untrained personnel should preferably not be taken into the production areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing.

1.11 Gowns used in production processes should be washed after production and should not shed particles. In addition, at least they should be ironed before used and kept in a proper clean place.

CHAPTER 2: PREMISES

3.1 Premises intended for hospital production of infusions (Infusion unit) should be designed to avoid unnecessary entry of personnel who are not involved in production activities.

3.2 The premises must be free from any source of contamination, e.g. from insects or faeces from small animals like lizards and rodents. Proper ventilation is necessary such as use of air conditioners (AC) of split unit type to reduce the risk of contamination.

3.3 Premises for an infusion unit should be designed to contain at least three rooms (i.e. material preparation/washing room, production room and sterilization room) that are adequate in size and follow flow-pattern of activities.

3.4 A changing room should be located just before entering the production area. Street clothes should not be brought into production room and personnel entering changing rooms should dress as per procedure using clean protective gears such as caps, masks, aprons, coats and gum boots.

3.5 Changing rooms can be designed as airlocks and located to separate the different rooms with respective operations, thus minimizing possible particulate and microbiological contamination of products under preparation and protective clothing in the production room.

3.6 Airlock doors should not be opened simultaneously.

3.7 Only clean ironed/sterilized or adequately sanitized protective garments should be provided. The use of disposable clothing may be necessary.

3.8 The aseptic preparation area should be designed, operated and managed so as to minimize microbial and particulate contamination. The aseptic preparation area should be a limited access area that is separated from other pharmacy operations.

3.9 The aseptic preparation area shall be clean and should be of sufficient size and well lit. Premises should be designed and maintained in a manner which will prevent entry of insect and migration of extraneous materials from outside.

3.10 Floors, walls or partitions and ceilings of the aseptic preparation area should be non-porous and washable so that they can be cleaned regularly, i.e. preferably tiled or at least oil painted. All exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated applications of cleaning agents and disinfectants.

3.11 Sinks and drains should be avoided and should be excluded from aseptic preparation areas wherever possible. Where installed they should be designed, located and maintained so as to minimize risks of microbial or foreign material contamination generated during sink usage.

3.12 Access to the aseptic preparation area should be limited. Individuals who are required to be in the area should be properly attired.

3.13 Refrigeration facilities and freezing capabilities where applicable should be available to store supplies which require low temperature.

3.14 Room for washing/cleaning primary packaging materials (i.e. glass bottles, rubber stoppers, etc.) for infusions production should be designed with hard work tops and provided with a minimum of three sinks for materials washing and preparations.

3.15 The washing room should be provided with hatch (small sliding window preferably made of aluminium material) or dynamic pass box to pass the cleaned primary packaging materials next to the production room. After the last rinsing in the cleaning process bottles should be transferred further upside down to avoid any contaminants entering the bottles.

3.16 Production room (clean room) should also be designed with hard work tops preferably of smooth-surfaced sealed cement or terrazzo.

3.17 Floor should be cemented, smooth and may be preferably of terrazzo or epoxy resins paint. Tiles are not encouraged as may be a source for harbouring the microbes because of inter-connections between tile pieces.

3.18 The room should be provided with hatch (small sliding window preferably made of aluminium material) or dynamic pass box to pass the filled- prepared infusions bottles to the next sterilization room. The room may be designed (with transparent glass material) such that operations being done can be observed from adjacent rooms. The actual filling process is preferably performed under a hood, ideally under a laminar flow cabinet.

3.19 Materials that rot such as wood which attract growth of moulds and other microbes should not be used and applied as finished construction material especially within the production room.

3.20 Water pre-treatment and purification system should be located/ installed out of clean rooms and piping system should be used to convey water to the production area where filling and sealing takes place.

3.21 Drains should be provided where possible and sinks should be avoided in production room (i.e. room where final filtration and bottling of infusions are done).

3.22 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

3.23 Ceiling board should be of hard board that does not absorb water/ humidity (e.g. plain aluminium sheet) and should be painted with oily paints preferably white or broken-whites that are water-washable.

3.24 False ceilings should be sealed to prevent contamination from the space above them.

CHAPTER 3: EQUIPMENT

3.1 Equipment such as tanks, carts and tables used in aseptic preparation area shall be made of material that is easily cleaned. Stainless steel is recommended.

3.2 The parts of production that come into contact with the product should not be reactive, additive or absorptive to an extent that it will affect the quality of the product and thus present any hazard.

3.3 Equipment surfaces that come into contact with sterile preparations should be properly cleaned and disinfected before placed in the production area.

3.4 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated accordingly.

3.5 Equipment repairs should be done outside the aseptic preparation area whenever possible. When it is not possible repairs should be followed by thorough cleaning and sanitation of the premises and the equipment.

3.6 All equipment, including sterilizers (autoclaves) and water-treatment system (Reverse Osmosis plant, deionizers, distillers) should be subject to planned preventive maintenance, validation and monitoring. The approval for use following maintenance work should be documented.

3.7 Equipment used for processing sterile products should be designed in such a way that it can be effectively sterilized by steam or other relevant method. For infusions prepared at hospital level, stainless steel 316 L grade containers (i.e. graduated stainless steel buckets, pressure vessels jugs etc.) are preferred.

3.8 Equipment fittings and services (e.g. autoclave maintenance) should be designed and installed in such a way that maintenance and repairs can be carried outside the clean area.

3.9 When equipment maintenance is carried out in the clean area (e.g. Reverse Osmosis machine maintenance, deionizer, and distiller), clean instruments and tools should be used and the area should be cleaned and disinfected again where appropriate before processing continues.

Sanitation

3.10 Hard surfaces should be regularly cleaned and disinfected in accordance with the written procedures.

3.11 Disinfectants and detergents should be selected and used to prevent microbial contamination. Diluted solutions should be kept in cleaned containers and they should not be stored for long periods unless sterilized and chemical stability has been established. Partly emptied containers should not be toped up. After the use of disinfectants and detergents verification must be performed that no residues of these substances remain in the cleaned equipment.

3.12 The sanitation and maintenance of hygienic condition in all areas of infusion unit premises is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written procedure.

3.13 Cleaning equipment like mops, sponges etc. are not appropriate for use in aseptic preparation areas. They should be made of materials that generate a low level of particles eg. Lint free cloth.

3.14 An appropriate method of disposing wastes should be established and documented; wastes should not accumulate in the preparation area.

Water Supply, pre – treatment and purification system

3.15 Water sources, water pre-treatment and purification system (i.e. pre- filtration by sand filters, deionizers, Reverse Osmosis membrane filtration system or distillation) for water for injection production should be monitored regularly for performance parameters and contamination to ensure that the water for injection complies with the specifications appropriate for its use i.e. according to pharmacopoeial standards. Records should be maintained of the results of monitoring and of any action taken.

3.16 Water for injection preparation/production at hospital level should be obtained from water purification systems e.g. deionizer, Reverse Osmosis system or distiller. Its 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.

3.17 A Quality Control testing mechanism for the maintenance of the water treatment system is mandatory.

3.18 Water for injection for the daily infusion preparation should be produced and used immediately for such a particular production day and should not be stored.

3.19 At least the first two litres of water for injection produced (after switching on the water treatment plant) should be discarded. This will minimize the risk of using leftover (remained) water in the pipe.

3.20 All pipes, hoses and tubes used during the purification process should be emptied, drained and dried whenever possible after the purification process.

CHAPTER 4: PRODUCTION

4.1 Only the minimum number of qualified personnel required should be present in production room.

4.2 In- and out-movements from production room, attending phone calls and any other activity that may negatively influence the product quality should be prohibited.

4.3 Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material or any other product that may compromise the quality of the manufactured product is restricted in the production areas.

4.4 In general, any unhygienic practice within the aseptic preparation area or in any other area where the product might be adversely affected should be forbidden.

4.5 Personnel should wash hands with detergent and apply suitable hand sanitizer at the beginning of their work and also when re-entering the aseptic preparation area.

4.6 Personnel should repeat the preparation process if contamination occurs.

4.7 Ingredients, vehicles and containers should be checked for defects, expiration dates, and damage before use.

4.8 All materials essential for production should be placed in the production area before processing.

4.9 Non sterile item surfaces should be disinfected with alcohol or other suitable antimicrobial agents before being placed into the production area.

4.10 Special and control measures should be placed where sterile components, raw materials or drug products are exposed.

4.11 No sterile product should be prepared unless its stability, compatibility, purpose and route of administration are judged appropriately by a pharmacist in charge. Master worksheets should be followed and any deviations from procedures appropriately documented and approved by the pharmacist incharge.

4.12 Manipulations required for the production of sterile preparations should be minimized by well established procedures.

4.13 Reconstituted powders should be mixed carefully to ensure complete dissolution of the drug.

4.14 Prepared solutions, in particular large-volume parenterals, should be immediately filtered through a microorganism-retaining filter (i.e. sintered glass filter or membrane filters) that is connected to a vacuum pump (should be oil-free) to supply positive pressure for filtration followed by subsequent filling and capping/closing process.

4.15 The storage tank for the bulk prepared aqueous solution should be stainless steel (SS 316 L).

4.16 The time between the start of the preparation i.e. water for injection collection and weighing of ingredients, dissolution, mixing, filtration through a bacteria-retaining filter (i.e. sintered glass filter or membrane filters) and its sterilization should be as short as possible appropriate to reduce microbial and other contamination.

Sterilization

4.17 Products made from non-sterile ingredients, an appropriate sterilization technique should be chosen to ensure that the physical and chemical integrity of the product is maintained.

4.18 Sterilization by moist heat (heating in an autoclave at 1200C equivalent to 2 bars for 20 minutes) is suitable only for water soluble ingredients and aqueous formulations. Both temperature and pressure have to be monitored in the process.

4.19 There should normally be an independent temperature indicator, (i.e. maximum temperature thermometer) the reading from which should be routinely checked against the set temperature (i.e. autoclave temperature gauge reading) recorded during the sterilization period/cycle.

4.20 The autoclave used for sterilization processes should be validated regularly to assure its performance.

4.21 The suitability of an autoclave used for IV fluids sterilization process should be demonstrated by physical measurements e.g. use inserted maximum thermometers in infusion bottle being sterilized and by biological indicators (autoclave tape) where appropriate.

4.22 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 must be kept.

4.23 The time between the start of the preparation of a solution and the sterilization of prepared product should be as short as possible.

4.24 Care should be taken to ensure that the steam used for sterilization is of suitable quality and does not contain contaminants at a level that could cause contamination of the product under sterilization or autoclave/equipment.

4.25 Use of purified water as a source of generating steam for autoclaving is recommended.

4.26 There should be clear segregation of the products that have not been sterilized from those that are already sterilized.

4.27 Each basket, tray or other carrier of products or components should be clearly labeled with the name of the prepared infusion, its batch number, and an indication of whether or not it has been sterilized.

4.28 Indicators such as biological indicator may be used, where appropriate, to indicate whether or not a prepared batch has passed thoroughly in the sterilization process.

4.29 Sterilization records should be available for each sterilization run/cycle. They should be approved as part of the batch-release procedure.

CHAPTER 5: QUALITY CONTROL

5.1 The sterility of the finished product (i.e. prepared infusions) is ensured by validation of the sterilization cycle in the case of terminally sterilized products.

5.2 Sterile finished products (sterile infusions) should be inspected individually for particulate contaminations/floating particles after sterilization.

5.3 When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background.

5.4 Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. The results should be recorded.

5.5 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 (worst case scenario) for example: for products that were heat sterilized in their final containers, consideration should be given to collect samples from the part of the load that was potentially the coolest part realized after conducting temperature mapping in the autoclave.

5.6 Pharmacopoeia methods for performance of the sterility test e.g. For hospital produced infusions, Pour Plate Method using Plate Count Agar should be conducted and results documented.

5.7 For large-volume prepared infusion solutions at hospital level, monitoring for endotoxins, using an established pharmacopoeia method (preferably by Limulus Amoebocyte Lysate (LAL) method) may be done at central or designated reference laboratory including any additional tests required for the finished product.

5.8 When a sample fails a test, the root cause analysis of such failure should be investigated and corrective action taken appropriately.

5.9 The pharmacist in charge should check the identity and the amount of ingredients in the sterile product versus the original prescription or master worksheet before the product is released.

Expiration dating

5.10 Expiration periods should be established for each type of sterile product.

5.11 Every sterile product should be clearly labelled with an expiration time and/or date.

5.12 Expiration periods should be derived using any or all of the following references:
a) manufacturers' recommendation
b) pharmaceutical compendia
c) professional literature and
d) in-house stability and/or sterility studies

5.13 Documentation to support the derivation of assigned expiration period should be available.

CHAPTER 6: LABELLING AND LABEL COMPONENTS

6.1 Sterile preparations should be labelled with the following information:
a) Batch number
b) Name and concentration of generic ingredients and vehicle
c) date of preparation
d) expiration date
e) route of administration
f) precautions
g) storage requirements

6.2 The label should be legible and affixed to the final container in a manner enabling it to be read while the sterile product is being administered.

6.3 The label should be checked by a pharmacist in-charge or delegate against the original order for accuracy and completeness.

6.4 Intermediate or in-process products should be clearly labelled and where appropriate the product or batch should be labelled to indicate the stage of production or status of the contents (e.g. quarantined, accepted, rejected).

6.5 Procedures should be instituted to ensure labels for different batches or products are separated and controlled so as to avoid mix up.

6.6 Hospitals cannot legally wholesale hospital prepared sterile formulations to another hospital or pharmacy unless they have authorization from TMDA.

Work contracted out

6.7 Some services/activities apart from production activities may be contracted out to another hospital or institution. Such services/activities include:
a) maintenance of the air handling system, water systems or other utility systems
b) maintenance of key equipment such as isolators, laminar air flow cabinets, sterilisers, balances
c) sterilisation of components and consumables such as mops, clothing, trays
d) supply of microbiological consumables (e.g. settle plates)
e) handling of waste
f) pest control
g) Quality control activities

6.8 These activities, if contracted out to a third party, could affect the quality of the products prepared. Therefore, there should be a written technical agreement between the hospital and contracted supplier.

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