World Health Organization

Assessment of Shelf Life and Storage Conditions of Registered Oxytocin in Southern African Development Community (SADC)

July 2021

Contents

List of Figures iii

List of Tables iii

Acknowledgements iv

Abbreviations and Acronyms v

EXECUTIVE SUMMARY VI

INTRODUCTION 1

Problem Statement 2

Objectives 3

Primary Objectives: 3

Secondary Objectives: 3

METHODOLOGY 3

Study Area 3

Study Design 4

Study Population 4

Sampling Method and Sample Size 4

Data Collection 4

Data Collection Methods and Instruments 4

Data Collection Process 5

Ethical Considerations 5

RESULTS 5

Institutional Details 5

Response Rate 6

Description of quality reviewers in the NRAs 6

Policies/Guidelines for assigning storage conditions and shelf life of medicines 6

Practices and key issues in assigning storage conditions and shelf life of products 6

Considerations of key issues when assigning storage conditions and shelf life 7

Requirements for conducting stability testing.....7

Considerations for approving storage conditions and shelf life and their importance.....8

Analysis of registered oxytocin products in participating countries.....12

DISCUSSION.....15

Limitations.....17

Conclusions and Recommendations.....18

REFERENCES.....19

ANNEXES.....21

Annexure 1: Introduction to the NRAs.....21

Annex 2: Survey Questionnaire.....22

Institutional Details.....22

Policies/Guidelines: Assigning approved storage conditions for registration applications.22

Procedures for assigning approved storage conditions and shelf life of products.....23

List of Figures

Fig. 1: Consideration of key issues in assigning shelf life and storage conditions.....7
Fig. 2: Minimum testing period for long term stability studies.....8
Fig. 3: Important considerations in the regulatory decisions on shelf life and storage conditions.....10
Fig. 4: Oxytocin registrations in SADC countries.....13
Fig. 5: Storage conditions of registered oxytocin products in SADC countries.....13
Fig. 6: Compliance with cold chain (2-8°C) and shelf-life requirements for registered oxytocin products in SADC countries.....14
Fig. 7: Proportion of registered products and the country of manufacture.....15

List of Tables

Table 1: Number of reviewers in the NRAs and average years of experience.....6
Table 2: NRA considerations in decision-making on storage conditions and shelf life.....9
Table 3: NRA approach to resolving conflict in considerations when approving storage conditions and shelf life.....11

Acknowledgements

The WHO Department of Sexual and Reproductive Health and Research, the Division of Access to Medicines and Health Products, and its Regulation Prequalification Department, gratefully acknowledge the contributions of Sibongile Mabuza in conducting this assessment as a consultant. This assessment was coordinated by Luther Gwaza, Rutendo Kuwana, and Mariana Widmer of World Health Organization (WHO). The authors also gratefully acknowledge the National Regulatory Authorities' contribution from Botswana, Democratic Republic of the Congo, Malawi, Mozambique, Namibia, South Africa, United Republic of Tanzania, Zambia, and Zimbabwe and the Heads of Regulatory Authorities in Southern Africa Development Community (SADC). This document was developed with the financial support of the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a cosponsored programme executed by the World Health Organization (WHO).

Abbreviations and Acronyms

EMA	European Medicines Agency
IDA	International Dispensary Association
LMICs	Low- and Middle-Income Countries
MAH	Market Authorization Holder
NCE	New Chemical Entity
NRA	National Medicines Regulatory Authority
PPH	Post-Partum Haemorrhage
SADC	Southern African Development Community
SRA	Stringent Regulatory Authority
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USFDA	United States Food & Drug Administration
WHO	World Health Organization

Executive Summary

Introduction

The value of oxytocin for various indications, including the prevention and treatment of postpartum haemorrhage (PPH), in obstetric practice, is well established. Historically, injectable oxytocin has generally been identified as a cold chain product; however, more recently, injectable oxytocin products approved for storage outside the refrigerator have become available in various markets. Therefore, in 2019 World Health Organization (WHO), United Nations Population Fund (UNFPA), and United Nations Children's Fund (UNICEF) issued a joint statement to provide clarity and guidance on the recommended storage conditions for oxytocin products. This statement confirmed that oxytocin products should be kept between 2-8°C during transportation and storage.

Despite the statement by the United Nations (UN) NRAs, national guidelines in many low- and middle-income countries (LMICs) contain limited or varied information on oxytocin storage conditions (Oliver et al., 2018). The practice of transporting and storing these products in hot, ambient temperature conditions for extended periods, therefore, continues even in climatic zones IV conditions. This results in oxytocin products that have a decreased assay content and increased related substances outside acceptable limits.

Further, the varied storage conditions (including storage at a temperature not exceeding 30°C) of approved products circulating in various countries imply that the national regulatory authorities (NRAs) of those countries may have approved these storage conditions. This raises questions about the stability data submitted to NRAs by the market authorization holders (MAHs), the robustness of the assessments, and decision-making on the storage conditions by the regulatory authorities.

Therefore, there is a need to assess the approved storage conditions and shelf life of oxytocin products in LMICs to examine the extent to which these conditions comply with the 2019 recommendations of the WHO-UNFPA-UNICEF Joint Statement.

The primary objectives of the assessment were as follows:

1. To establish the regulatory requirements, policies, and practices in SADC countries in establishing storage conditions and shelf life of medicines.

2. To establish the approved storage conditions and shelf life of oxytocin products registered in SADC countries.
3. To establish the extent to which oxytocin products registered in SADC countries comply with the WHO-UNFPA-UNICEF recommendation.

Methodology

This survey research evaluates the approved storage conditions and shelf life of oxytocin products registered and regulatory policies, requirements, and practices when assigning shelf life and storage conditions in ten Southern African Development Community (SADC) countries with active medicines registration systems. Six countries were excluded either due to non-active registration systems or considered high-income countries. Data were collected from the list of registered products available in the public domain or through focal persons. Additionally, an online survey to assess the policies, requirements, and practices of the NRAs was completed by nominated focal persons from each NRA. Data were analyzed in Microsoft Excel using descriptive statistics.

Summary of Findings

Seventy-one percent of oxytocin products registered in the nine SADC have an approved storage condition of 2-8˚C, which is in line with the WHO-UNFPA-UNICEF Joint Statement. These had different approved shelf lives, including 24 months (33%) and 36 months (31%). This is in line with the International Dispensary Association (IDA) and WHO guidelines which state that oxytocin products stored at 2-8˚C can be stored for up to 36 months. Six percent of the products had a shelf life of 60 months at 2-8˚C. The shelf life of one product with storage conditions of 2-8˚C could not be ascertained. Fourteen percent of products had non-cold chain storage conditions. These products were confined to two countries. The remaining 15% of products had unknown approved storage conditions; this information was not reported because it was unavailable for various reasons.

Conclusions and Recommendations

In conclusion, 65% of the oxytocin products approved by NRAs in the selected countries comply with the recommended shelf life (up to 36 months) under cold chain conditions (2-8˚C). However, the rest of the products (35%) are considered non-compliant with a shelf life exceeding 36 months at 2-8˚C, stored under room temperature, or unknown storage conditions.

There is a need for interventions in the two countries with registered oxytocin products with non-cold chain conditions focusing at policy level (adopting oxytocin specific policy aligned with the WHO-UNFPA-UNICEF Joint Statement) and technical level (training of reviewers). Moreover, although most countries had appropriate policies, requirements, and good review practices, training on decision models when assigning shelf life and storage conditions would enhance the robustness of the regulatory processes in SADC countries.

The study focused on approved products and countries with active registration systems; however, it is conceivable that products in the market may have different storage and shelf life conditions. Therefore, all the NRAs are recommended to adopt a policy on oxytocin storage conditions and shelf life to ensure that registered products and any donations or exemptions from registration comply with the cold chain requirements for oxytocin products. Further, post-marketing surveillance of oxytocin products in the SADC market will verify the quality of all available oxytocin products in the market and applicability of shelf life exceed 36 months when stored at 2 – 8°C.

Introduction

The WHO defines PPH as a blood loss of 500 ml or more within 24 hours after birth (Dept. Reproductive Health and Research, 2012). PPH has been predicted to cause approximately 20% of pregnancy-related deaths globally, most of which are in LMICs (Say et al., 2014). Although in its most recent recommendations, the WHO has increased the range of options of products that can be used for the prevention and treatment of PPH (Lambert et al., 2020), oxytocin injection, however, remains the most available, and therefore the drug of choice for the prevention and treatment of PPH in LMICs.

The value of oxytocin for various indications, including the prevention and treatment of PPH, in obstetric practice, is well established. Historically, injectable oxytocin has generally been identified as a cold chain product. Storage of this product between 2°C and 8°C prevents degradation. However, when oxytocin is exposed to high temperatures for extended periods, the potency of oxytocin decreases to below the acceptable limit of 90 percent of the labeled claim (Thakral et al., 2018).

Several studies have identified quality issues with oxytocin products sampled through the supply chain in different countries. Most of these studies have reported unacceptable levels of oxytocin in the products (Theunissen et al., 2018). The poor quality of these oxytocin products could be attributed to deficiencies in the manufacturing process. Still, more importantly, it is thought to be due to exposure to higher temperatures than what is acceptable for the products during storage and transportation (Lambert et al., 2020).

While the general recommendation is to store oxytocin between 2°C and 8°C, recommendations in different pharmacopoeia show that there is generally no consensus on the appropriate storage conditions for the Active Pharmaceutical ingredient (API) and the dosage form (Thakral et al., 2018). Based on a comprehensive study conducted by WHO in collaboration with the IDA Foundation in 1993, WHO recommends storage under refrigeration (2°C to 8°C) whenever possible (Hogerzeil et al., 1993). In this study, conditions of a tropical climate were simulated in the laboratory, and two batches of three brands of oxytocin ampoules were stored at different temperatures. Samples were assayed for oxytocin content over two years (Hogerzeil et al., 1993). The same study also concluded that it is acceptable to keep oxytocin injections unrefrigerated for short periods: no more than one month at 30°C, or one week at 40°C. In addition, WHO and IDA then also suggested the following guidelines for the shelf life of oxytocin injections stored at different temperatures:

- Maximum shelf life of 3 years at 2 - 8°C.
- Maximum shelf life of 2 years when stored below 21°C.
- At 25°C, the shelf life is reduced to 1 year.
- At 30°C, the shelf life is reduced to 6 months.
- At 40°C, a maximum of 1 week during transportation.

Like other medicines, oxytocin products should be stored according to the storage conditions approved by the respective NRAs in the target markets based on the evaluation of stability data provided by the MAH during the market authorization process.

Over the past twenty-five years, there have been several reports on oxytocin quality in LMIC; most publications have been released in the last five to seven years (Oliver et al., 2018). Several field studies showed decreased potency for oxytocin products, especially under tropical conditions (Hogerzeil et al., 1993). Therefore, concerns are frequently raised about the challenge of maintaining the effectiveness of oxytocin for PPH prevention in tropical settings when refrigerated storage conditions cannot be assured (Oliver et al., 2018). Several studies included products that were sampled from some SADC countries such as Zimbabwe (Hogerzeil et al., 1993), Tanzania (Nadkarni et al., 2018), the Democratic Republic of Congo (DRC) (Lambert et al., 2018), Malawi (Hagen et al., 2020) and Madagascar (Sabartova et al., 2015).

Policy discussions on the storage of oxytocin injection products among international health organizations have increased in recent years. In 2019, the WHO, UNFPA, and UNICEF released a joint statement stating that oxytocin products be kept in the cold chain (between 2 and 8 °C) during transportation and storage (Lambert et al., 2020). Despite this pronouncement, national guidelines in many LMICs often contain limited or varied information on oxytocin storage conditions (Oliver et al., 2018). As a result, these products are not being stored under cold chain conditions for extended periods, including in climatic zone III or IV countries.

Problem Statement

In 2019, WHO, UNFPA, and UNICEF issued a joint statement that provided clarity and guidance on the recommended storage conditions for oxytocin products. This statement confirmed the recommendation that these products should be stored at between 2-8°C. However, despite this statement by these UN NRAs, national guidelines in many LMICs contain limited or varied information on oxytocin storage conditions (Oliver et al., 2018).

This results in these products not being stored under cold chain conditions for extended periods, including in countries in climatic zone III or IV. In addition, the diverse recommended storage conditions on the labels of products circulating the markets of various countries imply that the NRAs of those countries may have approved these conditions.

Although several studies were done on the quality of oxytocin products in some SADC countries, there is a dearth of information on the approved storage and shelf life conditions and regulatory policies and decision-making approaches for oxytocin products in those settings. In other words, are the oxytocin-quality related issues due to regulatory inadequacy in those settings?

This study assessed the extent to which the storage and shelf life of approved oxytocin products in SADC comply with the WHO-UNFPA-UNICEF Joint Statement's recommendations. In addition, the regulatory requirements, policies, and practices in those settings were reviewed.

Objectives

Primary Objectives:

1. To establish the regulatory requirements, policies, and practices in SADC countries in establishing storage conditions and shelf life of medicines.
2. To establish the approved storage conditions and shelf life of oxytocin products registered in SADC countries.
3. To establish the extent to which oxytocin products registered in SADC countries comply with the WHO-UNFPA-UNICEF recommendation.

Secondary Objectives:

1. To assess the consistency in the container-closure system, storage, and shelf-life of the same product approved in several SADC countries.

The findings from the study would assist in the formulation of possible interventions to assist countries in ensuring that quality oxytocin products are always are available to the end-user.

Methodology

Study Area

The assessment was conducted in the SADC countries. Data were collected between August and December 2020.

Study Design

This descriptive survey study evaluates the approved storage conditions and shelf life of oxytocin products registered in the SADC countries, the extent of compliance with the WHO-UNFPA-UNICEF Joint Statement for the transportation and storage of oxytocin products.

Study Population

The problems with oxytocin were observed in LMICs with climatic zone III or IV, which is about 53% of the 194 WHO Member States. About 40% of these countries are in the WHO African Region, 20% in the Americas, 15% in the Western Pacific Region, 10% each in the Eastern Mediterranean and Southeast Asia Regions, and less than 5% in the European Region.

Sampling Method and Sample Size

The WHO African Region was selected as the target region based on the burden of the problem. Convenience sampling was employed in selecting the SADC region for the study. The region has sixteen countries (Angola, Botswana, Comoros, the Democratic Republic of the Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, United Republic of Tanzania, Zambia, and Zimbabwe), eleven classified as LMICs with climatic zone III or IV, two high-income countries (Mauritius and Seychelles were excluded in the study), and three countries with climatic zone II (included in the study). The study focused on regulatory outcomes; therefore, countries without an active medicines registration system at the time of the study were excluded from the study (Angola, Comoros, Eswatini, and Lesotho). The survey questionnaire was distributed to the ten eligible countries. The information was provided by officers working in the product registration department of the NRAs or Ministries of Health in each of these countries.

Data Collection

Data Collection Methods and Instruments

Data were collected using an online survey questionnaire ***(Annexure 2)*** distributed to nominated focal persons in the NRAs or Ministries of Health. In addition, an excel data extraction tool was used to collect data on the specific oxytocin products on the register of each participating country either through the online medicines register on the NRA's website

or completed by nominated focal persons in cases where no online medicines register was available. Only data on oxytocin products that were actively registered at the time of the study were considered.

The online survey was developed in English and translated into French for French-speaking countries.

Data Collection Process

Approved oxytocin-containing products were identified by the search term "oxytocin" from registered medicines for those countries with online medicines registers accessible to the public. The following information was extracted from the medicine registers: country of registration, NRA, product name, the name of the marketing authorization holder, the name of the manufacturer of the product, product registration number, date of registration, description of the container closure, approved storage conditions and approved shelf life. The information from the online medicine registers was supplemented with other sources of information, including the focal persons in each NRA. Focal persons completed the excel data extraction document for those countries without a medicine register accessible online at the time of the study.

An online survey questionnaire was used to collect information on policies, guidelines, procedures, and practices related to reviewing and assigning storage conditions and shelf life during the product registration process.

Ethical Considerations

Consent: No individual/person data were collected during the study. Permission to conduct the study was received from the Heads of NRAs of the SADC NRAs participating in the study.

Confidentiality: Publicly available data or data published as part of the product information were collected in the study. No confidential manufacturer information was collected. For confidentiality reasons, the manufacturers and NRAs are anonymized.

Nonmaleficence (do no harm): The respondents to this assessment study were not exposed to any harm, neither were the institutions in which they work.

Results

Institutional Details

This section summarises the institutional details of the NRAs that participated in the study. In addition, the summary includes the response rate, details on the reviewing staff in the NRA's product evaluation and registration departments.

Response Rate

The survey questionnaire was distributed to the ten eligible countries, and responses were received from nine countries (90%), and eight countries (80%) verified or completed the data extraction tool.

Description of quality reviewers in the NRAs

Table 1 shows the number of total reviewers per NRA, those reviewing quality data, and the mean years of experience of the reviewers. There were 183 reviewers in the nine countries with a total population of 290 million people (ranging from 2 million each in Botswana and Namibia to 87 million in the Democratic Republic of the Congo), giving a reviewer/population ratio of 0.63.

Table 1: Number of reviewers in the NRAs and average years of experience

	Total number of reviewers in the NRAs	**Number of quality reviewers**	**Years of experience**
Average (SD)	20.33 (15.61)	17.67 (16.06)	6.22 (3.76)
Range	3 – 55	0 - 55	2 - 15

Policies/Guidelines for assigning storage conditions and shelf life of medicines

Most Member States who participated in the study have general policies/guidelines for assigning storage conditions (seven countries) and shelf life (six countries) for medicines. However, none of these countries have a specific policy or guideline for oxytocin products, except two NRAs that confirmed having a specific policy or guideline for assigning shelf life for oxytocin.

Practices and key issues in assigning storage conditions and shelf life of products

The findings in this section show the standard procedures and practices in assigning storage conditions and shelf life by the institutions that responded to the survey. The summary findings show the key issues, importance, and the frequency that these key issues are considered in practice, requirements for the number of batches for stability studies, requirements for the conditions at which stability testing should be done, requirements for the

minimum testing period for long term stability studies, and the acceptability of extrapolation in assigning shelf life.

Considerations of key issues when assigning storage conditions and shelf life

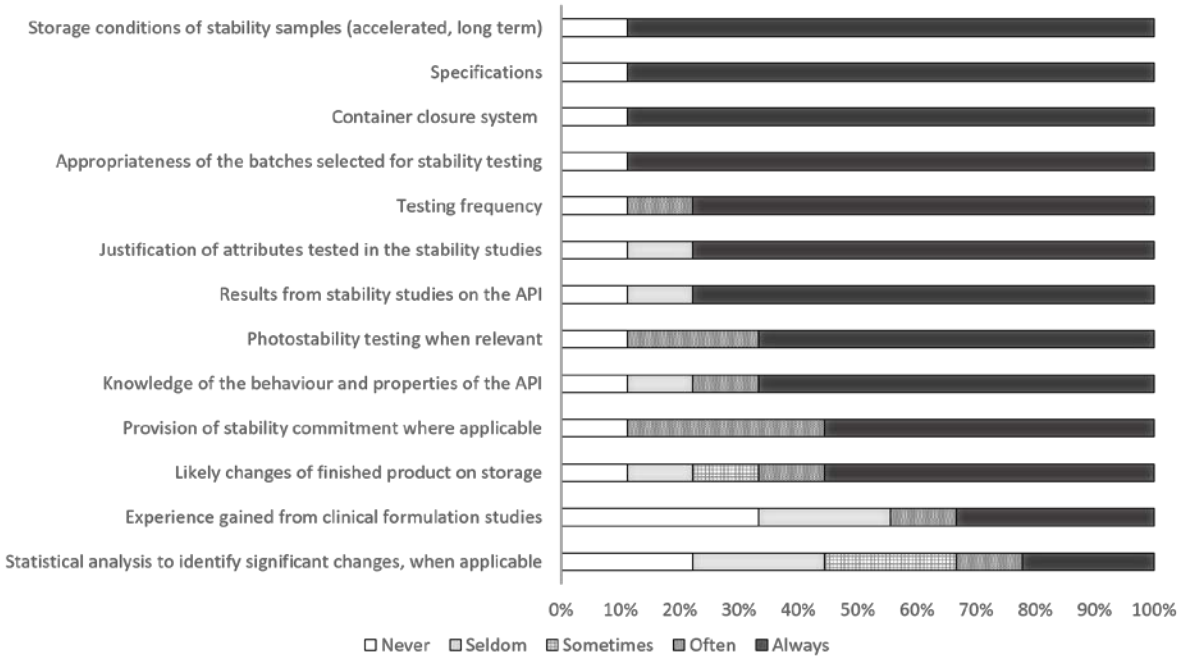

Fig. 1: Consideration of key issues in assigning shelf life and storage conditions

Fig. 1 shows that in more than 50% of the NRAs, all the key issues are always considered when assigning storage conditions and shelf life, except statistical analysis to identify significant changes and experience gain from clinical formulation studies. Most NRAs, except one, always consider storage conditions of stability samples, specifications, container closure system, and appropriateness of the batches used for stability studies when assigning shelf life. Areas with variable practices among the NRAs were photostability testing, when relevant, knowledge of the behaviour and properties of the active pharmaceutical ingredient (API), provision of stability commitment, when applicable, and likely changes of the finished product on storage. What is also of note is that at least one NRA ignores the specified issue in the decision-making.

Requirements for conducting stability testing

A majority (78%) of the NRAs require three production-scale batches for stability studies, while the remainder require two batches. For products stored at ambient conditions, appropriate stability testing conditions are applied by all countries for accelerated and long-term based on the climatic conditions for the respective country. However, for products that

require storage at 2 – 8°C, one country appears not to require or apply the appropriate testing conditions under accelerated and long-term stability testing.

Fig. 2 shows that the minimum testing period for long-term stability studies required by most NRAs is 12 or 36 months. There were, however, those NRAs who had other requirements, or the requirements were not specified. The NRA with a different requirement stated that *"a new chemical entity (NCE) should have a minimum testing period of 12 months for long term stability studies and nine months for generics or well-known chemical entities"*.

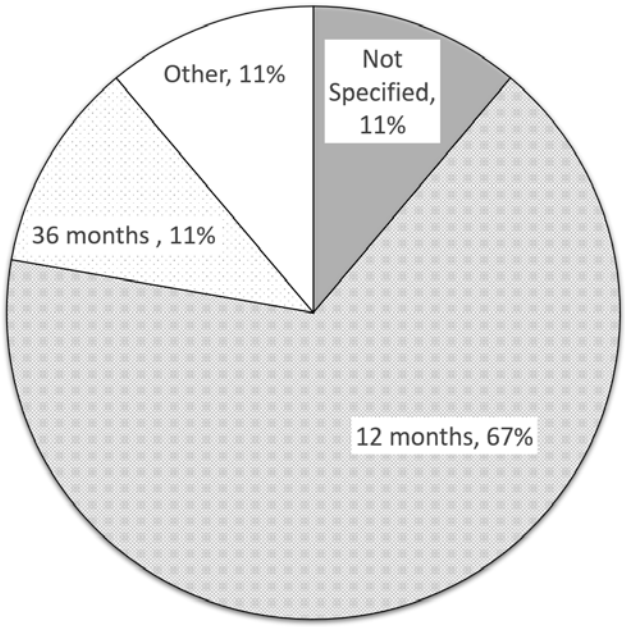

Fig. 2: Minimum testing period for long term stability studies

Considerations for approving storage conditions and shelf life and their importance

Table 2 shows that all NRAs that participated always consider the data submitted by the applicant when assigning storage conditions and shelf life and assign greater importance to these data in the regulatory decision-making (***Fig.*** 3). Decisions or guidance from other organizations or institutions is also another key important consideration during this process. Prior decisions in the NRA on similar products or those decisions made in other NRAs on similar products are less likely to be considered; in fact, the findings show that prior decisions in the NRA on similar products are the least likely to be considered during this decision-making process.

Table 2: NRA considerations in decision-making on storage conditions and shelf life

	Always considered	**Often considered**	**Considered about half the time**	**Seldom considered**	**Never considered**
Data in the submission	100%	0%	0%	0%	0%
Prior decisions in the NRA on similar products	22%	0%	11%	44%	22%
Decisions made in other NRAs on similar products	11%	22%	11%	44%	11%
Decisions /guidance from other institutions	78%	11%	0%	11%	0%

The findings also indicate that 67% of the NRAs that participated had other considerations when approving storage conditions and shelf life other than those specified. These considerations included *"whether the molecule is a new chemical entity (NCE) or well-known chemical entity (generic) as well as whether the molecule is in the recognized pharmacopeia or not, the data in the in-use stability study report for some products like solutions which are used multiple times and how facilities are likely to store the products, such as, vaccines for mass administration".*

In addition, the findings also show that extrapolation of shelf life is acceptable in all the NRAs that responded to the survey.

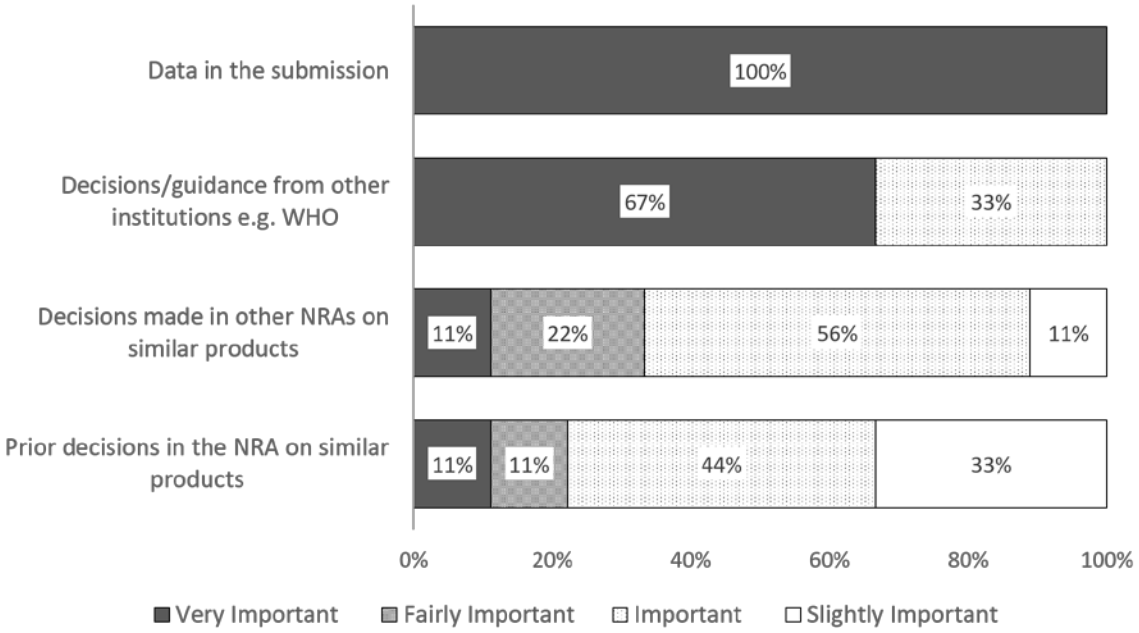

Fig. 3: Important considerations in the regulatory decisions on shelf life and storage conditions

When there is conflict in the considerations listed in ***Table*** 2 and ***Fig.*** 3, the approach of the NRAs in decision-making is shown in ***Table*** 3. WHO recommendations tend to have a lot of influence on the regulatory decision when there is a conflict, followed by the data submitted by the applicant. Other considerations stated by the NRAs include "*decisions by regulatory authorities with higher maturity level, such as USFDA, EMA"*, or "*decisions made at the regional level, Zazibona, in similar circumstances"*. However, the other considerations were only slightly important when approving storage conditions and shelf life.

Table 3: NRA approach to resolving conflict in considerations when approving storage conditions and shelf life

Scenarios	Accept store below 30°C	Accept store at 2-8°C	Reject the application	Other
a) Data in the submission shows the product is heat stable (for example, store below 30°C), but other NRAs do not accept heat-stable formulations (that is, accept products for storage at 2-8°C).	78%	22%	0%	0%
b) Data in the submission shows the product is heat stable (for example, store below 30°C), but WHO recommendations specify store in the refrigerator (that is, store at 2-8°C).	22%	78%	0%	0%
c) Other NRAs have registered the product as a heat-stable product (that is, store below 30°C). Still, data in the submission shows the product is unstable at 30°C and should possibly be stored in the refrigerator (2-8°C).	11%	78%	11%	0%
d) WHO recommendations consider the product as being a heat-stable product (that is, store below 30°C), but data in the submission shows the product is unstable at 30°C and should possibly be stored in the refrigerator (2-8°C).	11%	78%	0%	11%
e) Data in the submission shows the product is heat stable (that is, store below 30°C), but prior decisions and products had "store in the refrigerator (2-8°C)".	67%	22%	0%	11%
f) Data in the submission shows the product should be stored in the refrigerator (2-8°C), but prior decisions and products had the product as being heat-stable (that is, store below 30°C).	33%	56%	0%	11%

Analysis of registered oxytocin products in participating countries

This section summarizes the findings on registered oxytocin products in the participating SADC countries that responded to this part of the survey. The total registered products in the SADC countries ranged from four to ten (Fig. 4), with 48 registered products in eight countries. Seventy-one percent of the products had storage conditions of 2-8°C, consistent with the WHO-UNFPA-UNICEF Joint Statement. Fourteen percent had other approved storage conditions, while storage conditions for fifteen percent of the products were unknown. Four countries (Democratic Republic of Congo, Namibia, United Republic of Tanzania (the), and Zimbabwe) had approved storage conditions of 2 – 8°C for all the registered products, two countries (Botswana and South Africa) had some products with unknown storage conditions because the products were registered a long time ago and the information was not easily accessible. In comparison, two countries (Malawi and Mozambique) had some products with other non-cold chain storage conditions (Fig. 5). The products with "other approved non-cold chain storage conditions" included the following conditions:

- "The product should be stored in a cool, dry & dark place."
- "Store at a temperature between 2°C and 15°C. Do not freeze."
- "Keep in a dry place, protect from moisture, light, at the temperature not exceeding 30°C."
- Store below 25°C
- 25°C

Sixty-five percent of the registered oxytocin products comply with the cold chain storage and shelf-life requirements, while 21% were non-compliant, and 15% had incomplete information (Fig. 6). Comply with requirements means products with cold chain storage conditions (2-8°C) and shelf life of 24 or 36 months. Non—compliant products are products with non-cold chain storage conditions or shelf life exceeding 36 months.

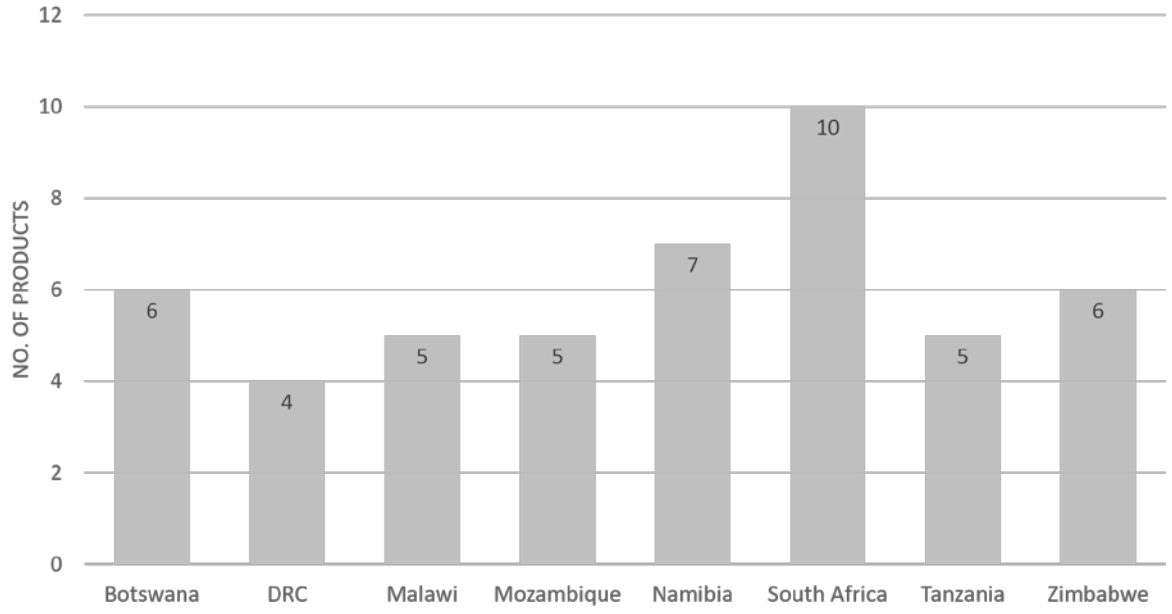

Fig. 4: Oxytocin registrations in SADC countries

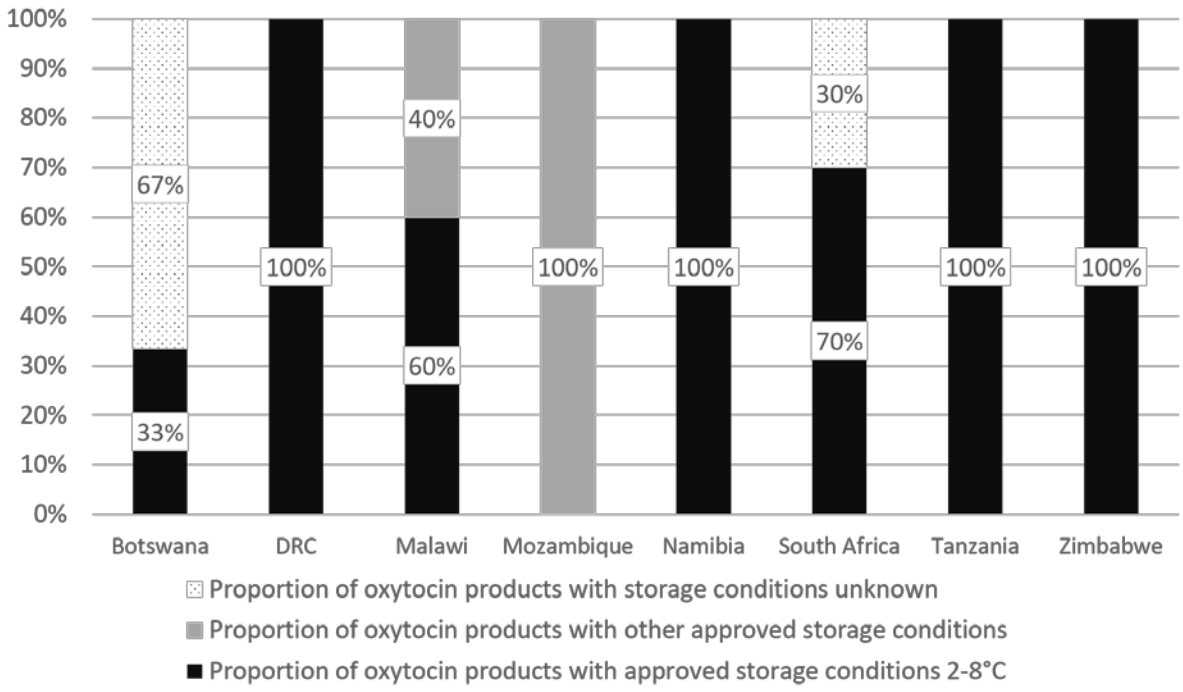

Fig. 5: Storage conditions of registered oxytocin products in SADC countries

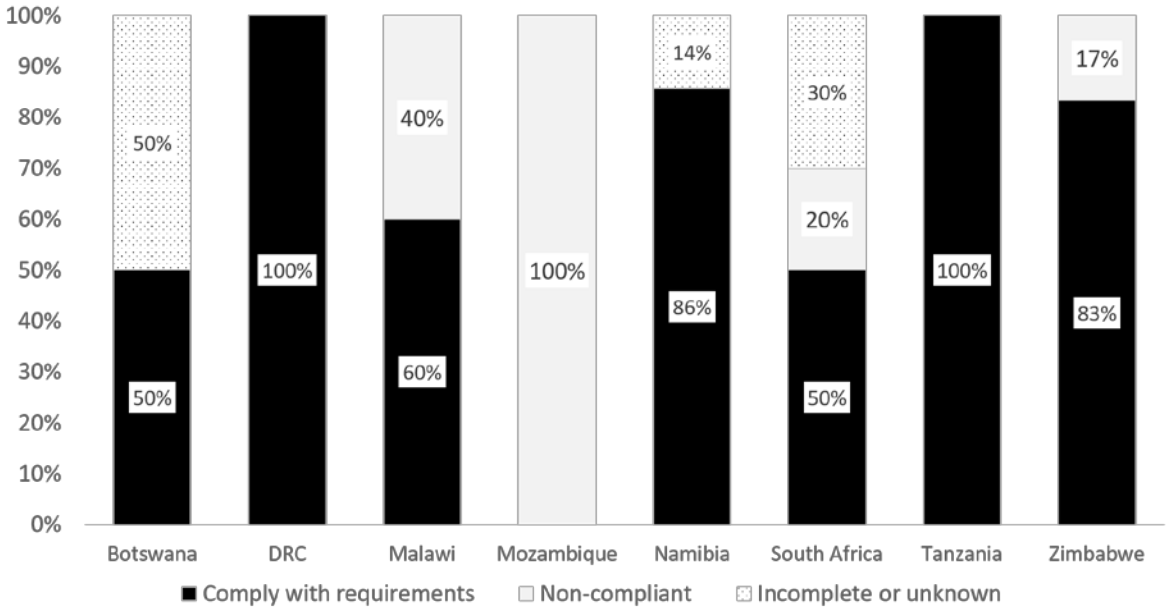

Fig. 6: Compliance with cold chain (2-8°C) and shelf-life requirements for registered oxytocin products in SADC countries

The 21 manufacturers of the registered oxytocin products were in seven countries. Fig. 7 shows the proportion of products manufactured in each of the seven countries. Four of the 21 (19%) manufacturers had six oxytocin products, among them registered in more than one country. All the commonly registered products had a similar container-closure system (Type 1 glass ampoule), and the recommended storage conditions of 2 – 8°C, except one product with a store below 25°C. One product was registered in four countries, one in three countries, and four were registered in two countries. Seven countries had at least one product in common with one or more countries. The marketing authorization holders varied across the countries.

Although the registration conditions for products approved in more than one country were similar, the description of the container closure system and storage statements were not harmonized. For example, some of the statements were - "*Store between the temperature of 2˚C to 8˚C*", "*Store in the fridge 2 °C to 8 °C*", and "*Store in a refrigerator between 2 and 8 °C. Protect from direct light.*" The approved shelf-life was generally the same across countries for the same product; however, one product had a shelf life of 36 months in one country and 60 months in another country.

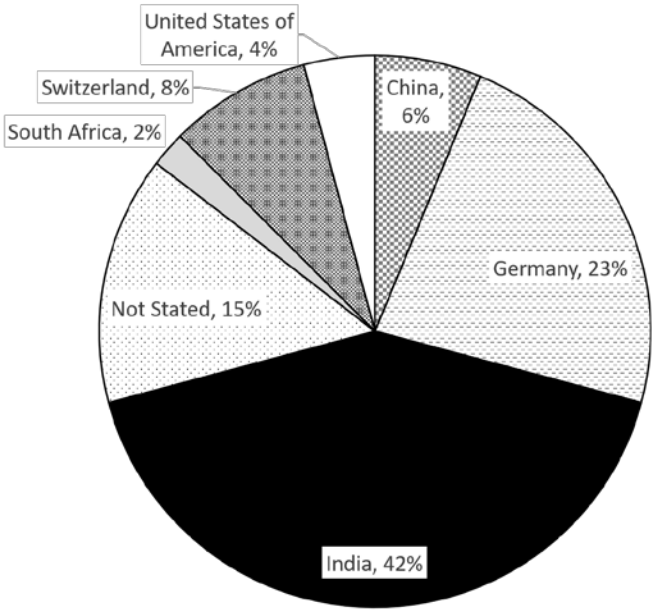

Fig. 7: Proportion of registered products and the country of manufacture.

Discussion

Although most NRAs confirmed the existence of general policy or guidelines for assigning storage conditions or shelf life, none of the countries had an oxytocin-specific policy or guideline. In other words, despite the WHO-UNFPA-UNICEF Joint Statement on oxytocin, the NRAs or Ministries of Health have not adopted this policy in practice.

Sixty-five percent of the registered oxytocin products in the eight SADC countries comply with the cold chain storage conditions of 2-8°C and shelf-life requirements, not exceeding 36 months consistent with the WHO-UNFPA-UNICEF Joint Statement that recommends that "*oxytocin products should be kept in the cold chain (between 2 and 8 °C) during transportation and storage"* (Lambert et al., 2020). Four of the eight countries had approved storage conditions of 2 – 8°C for all the registered products. In these countries, it can be inferred that any non-compliant products found in the market are most likely unregistered products.

Two countries had some products with unknown storage conditions because the products were registered a long time ago, and the information was not easily accessible. In comparison, only two countries (Malawi and Mozambique) had some products with other non-cold chain storage conditions, with all the five registered products having non-cold storage conditions. The observed non-compliance with some products in some countries supports the claim that despite the statement issued by WHO, UNFPA, and UNICEF, there

are still oxytocin products with different recommended storage conditions on their labels, including storage at < 25º C or < 30º C (Sabartova et al., 2015). The existence of divergent storage conditions for oxytocin products creates confusion on oxytocin's appropriate handling and storage, despite many studies indicating reduced potency when oxytocin is exposed to high temperatures for extended periods (Thakral et al., 2018).

The quality of oxytocin products partly depends on storage conditions and the length of the storage period, with a general recommendation of not exceeding 36 months when stored at 2 – 8°C. Storage at higher temperatures reduces the shelf-life. In this study, three products in two countries have an approved shelf life of 60 months at 2 – 8°C. Although this study considered shelf-life exceeding 36 months as non-compliant, the appropriateness of the shelf life beyond 36 months is difficult to conclude without examining the related stability data submitted to the respective NRAs. The local requirements, practices, and decision-making approaches of the NRAs should be considered in finding the way forward as the products considered non-compliant with the WHO-UNFPA-UNICEF Joint Statement are legally registered and compliant with the NRA's requirements. Also, other mature NRAs approved oxytocin products with non-cold chain conditions.

From this study, all the NRAs consider the data in the submission as the most important consideration when approving storage conditions and assigning shelf life during the products registration process. Other factors are considered but carry less weight compared to the data in the submission. The wide range of oxytocin products from different manufacturers come with varying storage and shelf life conditions. Coupled with the fact that all the NRAs do not have an oxytocin-specific policy for assigning shelf life and storage conditions, this may partly explain the divergent outcomes on registered oxytocin products. Adopting an oxytocin-specific policy is a potential strategy for NRAs to ensure that all available oxytocin products in their markets comply with cold chain conditions, limiting potential quality issues in the supply chain.

Notwithstanding the absence of an oxytocin-specific policy, good review practices and competence should lead to appropriate regulatory decisions that account for all available information and factors likely to impact regulatory decisions when assigning shelf life and storage conditions for any product, including oxytocin. Most of the surveyed countries apply the correct stability testing requirements, consider the key issues when reviewing stability data, and assigning shelf life and storage conditions.

However, considering the complexity with oxytocin, a product with many publications on quality-related issues, in some surveyed countries, the limited experience of some reviewers, and potential regulatory burden due to an imbalance between workload and the number of reviewers, is likely to contribute to a non-robust review and decision-making process, leading to approval of non-cold chain conditions or shelf life exceeding 36 months. For example, prior decisions and decisions from other NRAs are always considered by two and one NRA, respectively. This potentially explains the varying conditions of oxytocin approved in the same jurisdiction and among countries. Also, learning opportunities addressing issues such as photostability testing, knowledge of the behaviour and properties of the API, likely changes of the finished product on storage, extrapolation of stability results could enhance the competence of the reviewers in reviewing stability data and assigning appropriate storage conditions and shelf life.

Analysis of the marketed products showed that six countries shared commonalities in the similarity of products in their markets. The study showed that all manufacturers with products in different countries had approved storage conditions consistent in all the countries (2-8ºC). These conditions were also aligned to the WHO-UNFPA-UNICEF Joint Statement. The consistency in the outcomes implies applying appropriate policies/guidelines by the regulators and submitting the same data package by the applicants/manufacturers facilitate the same outcomes on storage conditions. However, there were some variations in shelf-life for two products, storage statements, and description of the container-closure for the same product registered in at least two countries. Implementing harmonized labelling requirements, including standard storage statements and description of container-closure systems, and inclusion of manufacturer details facilitates public confirmation of similarity of approved products.

Limitations

The study used convenience sampling, limiting the generalizability of the findings to other LMICs settings with climatic zones III and IV. Also, geographic regions may differ in practices and range of products approved in those settings; therefore, extrapolating the results from one African region to other regions in Africa or elsewhere should be done cautiously. Data on policies, guidelines, or procedures were not independently verified with source documents; instead, the study relied on feedback provided by focal persons through the online survey questionnaire. Interpretation of requirements and application of institutional

policies may vary depending on the individual completing the survey, their experience, and level of Authority within the NRA. The respondents varied in their positions, roles, and experience.

Nonetheless, the survey questions focused on objective practices based on written policies or documents rather than respondents' opinions to minimize bias. As a descriptive study, we can only infer correlation; however, the causes of approvals of oxytocin products outside the recommended storage and shelf-life conditions are yet to be determined. For instance, it is unclear whether the non-compliances are due to assessor competencies in reviewing the submitted data, lack of policies governing the shelf-life and storage of oxytocin at the country/NRA level, or both.

Unfortunately, copies of the policies or guidelines were not provided, although this was requested as part of the data collection. Therefore, the researchers could not independently verify oxytocin-specific policies or guidelines for assigning shelf life in the two countries that responded in the affirmative.

Conclusions and Recommendations

The majority (65%) of oxytocin products registered in the eight SADC countries had approved the storage conditions of 2-8˚C and shelf life not exceeding 36 months; thus, consistent with the WHO-UNFPA-UNICEF Joint Statement, which emphasizes that oxytocin products should be stored under cold chain conditions. Two countries (Malawi and Mozambique) had oxytocin products with non-cold chain storage conditions. There is a need for interventions in the two countries with registered oxytocin products with non-cold chain conditions focusing at policy level (adopting oxytocin specific policy aligned with the WHO-UNFPA-UNICEF Joint Statement) and technical level (training of reviewers).

Two countries (South Africa and Zimbabwe) had some products with a shelf life exceeding 36 months at 2 – 8˚C. Although stability data in the submission may support this, given the complexity and quality issues of oxytocin, there is a need to ensure that the quality of these products is maintained throughout the approved shelf life, for example, through targeted post-marketing surveillance and testing of the products throughout the supply chain in the market at the end of the shelf life.

For the most part, the NRAs have appropriate policies, regulations, and good review practices; nonetheless, adopting oxytocin specific policy, standard harmonized storage

statements, and description of the container-closure system, training on decision-models when assigning storage conditions and shelf life could ensure consistency in the reviews and outcomes for oxytocin products.

The study focused on approved products and countries with active registration systems; however, it is conceivable that products in the market may have different storage and shelf life conditions. Therefore, a policy on oxytocin storage conditions and shelf life will ensure that registered products and any donations or exemptions from registration comply with the policy to maintain a cold chain for oxytocin products. Further, post-marketing surveillance of oxytocin products in the SADC market will verify the quality of all available oxytocin products in the market.

References

1. Dept. of Reproductive Health and Research, W. (2012). WHO recommendations for the prevention and treatment of postpartum haemorrhage. In *World Health Organization*. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/

2. Hagen, N., Khuluza, F., & Heide, L. (2020). Quality, availability, and storage conditions of oxytocin and misoprostol in Malawi. *BMC Pregnancy and Childbirth*, *20*(184), 18. https://doi.org/10.1186/s12884-020-2810-9

3. Hogerzeil, H. V., Walker, G. J. A., & de Goeje, M. J. (1993). *Stability of Injectable Oxytocics in Tropical Climates*. https://apps.who.int/iris/bitstream/handle/10665/59411/WHO_DAP_93.6.pdf;jsessionid=45961148239412D32FE57C078646849C?sequence=1

4. Lambert, P., Mcintosh, M. P., Widmer, M., Evans, L., Rauscher, M., Kuwana, R., Theunissen, F., Yeager, B., & Petach, H. (2020). Oxytocin quality : evidence to support updated global recommendations on oxytocin for postpartum hemorrhage. *Journal of Pharmaceutical Policy and Practice*, *13*(14), 1–13.

5. Lambert, P., Nguyen, T.-H., Mcevoy, C., Singh Minhas, R., Wright, P., Deadman, K., Mulimbalimba Masururu, L., & Mcintosh, M. P. (2018). quality of oxytocin ampoules available in health care facilities in the Democratic Republic of Congo: an exploratory study in five provinces. *PAPERS*, *8*(2), 6. https://doi.org/10.7189/jogh.08.020415

6. Nadkarni, D., Gravelyn, S., Brova, M., Rashid, S., Yee, R., Guttieres, D., Clifford, K., Desai, D., & Zaman, M. (2018). Modeling patient access to therapeutic oxytocin in Zanzibar, Tanzania. *BMC Health Services Research*, *18*(645), 10. https://doi.org/10.1186/s12913-018-3452-8

7. Oliver, V. L., Lambert, P. A., Than, K. K., Mohamed, Y., Luchters, S., Verma, S., Yadav, R., Kumar, V., Teklu, A. M., Tolera, M., Minaye, A., & Mcintosh, M. P. (2018). Knowledge, perception, and practice towards oxytocin stability and quality: A qualitative study of stakeholders in three resource-limited countries. *PLOS One Open Access*, *13*(9), 16. https://doi.org/10.1371/journal.pone.0203810

8. Sabartova, J., Smid, M., & Mubangizi, D. (2015). Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children. http://www.who.int

9. Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, A.-B., Daniels, J., Gülmezoglu, M., Temmerman, M., & Alkema, L. (2014). Articles Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health*, *2*(6), e323–e333. https://doi.org/10.1016/S2214-109X(14)70227-X

10. Thakral, S., Suryanarayanan, R., Evans, L., & Nkansah, P. (2018). Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review About PQM. https://www.usp-pqm.org/sites/default/files/pqms/article/stability-storage-oxytocin-jul2018.pdf

11. Theunissen, F., Cleps, I., Chinery, L., Bochaton, F., & Vemer, H. D. (2018). *Oxytocin Quality-Evidence for Action*. https://www.conceptfoundation.org/wp-content/uploads/2018/03/Oxytocin-Quality-Evidence-for-Action.pdf

Annexes

Annexure 1: Introduction to the NRAs

Regulatory Assessment of Oxytocin Products in SADC Countries

Thank you for taking the time to respond to this short survey on the oxytocin products registered for marketing by your Authority.

This is a survey being conducted in the SADC Member States with the support of the Reproductive Health and Research Department and the Regulation and Safety Unit of the World Health Organisation (WHO). The objective of this assessment is to establish the labelling and storage conditions of oxytocin products registered (or those procured through government tenders/donors) in the SADC Member States. It also aims to establish the extent to which the said conditions in these products comply with the labelling and storage conditions for oxytocin products as per the 2019 WHO-UNFPA-UNICEF statement. The findings of this assessment will be used in an aggregated manner to support the Member States to formulate appropriate individual and collective interventions that will ensure that quality oxytocin products are always are available to the end-user.

Completing this questionnaire should take you about 10 minutes. Kindly remember also to complete the template on the list of oxytocin products registered in your country.

Should you have any questions connected to this assessment, kindly direct them to:

WHO

Your support of this project is appreciated in advance

Annex 2: Survey Questionnaire

Institutional Details

This group of questions aims to establish general information about the medicine's regulatory Authority.

Question 1: Name of Medicines Authority

Question 2: Country

Question 3: Number of Assessors in Authority

Question 4: Number of assessors assigned to do quality assessments only

Question 5: Designation of Respondent

Question 6: Number of Years Respondent has worked in the Authority

Policies/Guidelines: Assigning approved storage conditions for registration applications

This group of questions seeks to establish whether the medicines authority has documented policies/guidelines for assigning the approved storage conditions for finished product registration applications

Question 7: The NRA has a documented policy/guideline that is used for assigning the approved storage conditions for the finished product in registration applications

(If Yes, kindly attach a copy as per provision in question 8)

- Yes
- No

Question 8: Attach a copy of the policy/guideline that is used for assigning the approved storage conditions for the finished product in registration applications

Question 9: The NRA has a documented policy/guideline that is used for assigning the shelf life for the finished product in registration applications

(If Yes, kindly attach a copy as per provision in Question 10)

- Yes
- No

Question 10: Attach a copy of the policy/guideline that is used for assigning the shelf life for the finished product in registration applications

Question 11: For registration application, if your NRA has a documented policy/guideline used specifically for assigning the approved storage conditions for the oxytocin products, select the dot market yes below?

(If Yes, kindly attach a copy as per provision in Question 12)

Yes

Question 12: Attach a copy of the policy/guideline that is used specifically for assigning the approved storage conditions for the oxytocin products in registration applications

Question 13: The NRA has a documented policy/guideline used specifically to assign the shelf life for oxytocin products in registration applications.

(If Yes, kindly attach a copy as per provision in Question 14)

Yes

No

Question 14: Attach a copy of the policy/guideline used specifically to assign the shelf life for applications of oxytocin products in registration applications.

Procedures for assigning approved storage conditions and shelf life of products

This group of questions will assess the standard procedures used within your institution for assigning storage conditions and shelf life.

Question 15: The procedures used for assigning approved storage conditions and shelf life for a finished product in the NRA considers the following:

	Never	Seldom	Sometimes	Often	Always
Knowledge of the behaviours and properties of the API					
Results from stability studies on the API					
Experience gained from clinical formulation studies					
Likely changes of the finished product on storage					
The appropriate rationale for the selection of					

attributes to be tested in the formal stability studies					
Photostability testing has been conducted where appropriate					
The batches selected for stability testing are appropriate					
Container closure system					
Specifications					
Testing frequency					
Storage conditions of stability samples (accelerated, long term)					
Where necessary doing formal statistical analysis to identify significant changes					
Provision of stability commitment where applicable					

Question 16:State requirements in your NRA for the number of batches for stability studies.

- Not Specified
- One batch
- Two batches
- Three batches
- Four or more batches

Question 17: State requirements in your NRA for the conditions at which stability testing should be done.

	Always Considered (routine practice for all products, as appropriate)	Often Considered (generally followed for most products, as appropriate)	Considered About Half the Time as appropriate for products	Seldom Considered (followed for a few products, as appropriate)	Never Considered (not followed at all)
Not Specified					
Stress testing as appropriate for the individual API and type of FPP involved					
Accelerated (Ambient) 40°C ± 2 °C/75 % RH ± 5%					
Accelerated (Refrigerated) 25°C ± 2 °C/60 % RH ± 5%					
Accelerated (Frozen)					

5°C ± 3°C					
Intermediate 30°C ± 2 °C/65 % RH ± 5%					
Long Term 25°C ± 2 °C/60 % RH ± 5%					
Long Term 30°C ± 2 °C/35 % RH ± 5%					
Long Term 30°C ± 2 °C/65 % RH ± 5%					
Long Term 30°C ± 2 °C/75 % RH ± 5%					
Long Term (Refrigerated) 5°C ± 3 °C					
Long Term (Frozen) -15°C ± 5 °C					

Question 18: State requirements in your NRA for the minimum testing period for long-term stability studies.

- Not Specified
- Three months
- Six months
- 12 months
- 24 months
- 36 months
- Other

Question 19: State whether extrapolation is acceptable to assigning shelf life.

- Yes
- No

Question 20: In approving storage conditions and shelf-life in the NRA, we consider:

	Always Considered (routine practice for all products)	Often Considered (generally followed for most products)	Considered About Half the Time	Seldom Considered (followed for a few products)	Never Considered (not followed at all)
Data in the submission					
Prior decisions in the NRA on similar products					
Decisions made in other NRAs on similar products					
Decisions/guidance from other organizations/institutions, for example, WHO					

Question 21: In your NRA, what else do you consider in approving a finished product's storage conditions and shelf-life.

Question 22: For each of the considerations, indicate the importance of each through the following scale:

	Very Important	Fairly Important	Important	Slightly Important	Not Important at all
Data in the submission					
Prior decisions in the NRA on similar products					
Decisions made in other NRAs on similar products					
Decisions/guidance from other organizations/institutions, for example, WHO					
Other					

Question 23: In cases where there is conflict in the considerations that are used in approving storage conditions and assigning shelf life, for example, in the following scenarios: How would do you usually resolve this conflict?

	Accept store below 30°C	Accept store at 2-8°C	Reject the application	Other
a) Data in the submission shows the product is heat stable (for example, store below 30°C), but other NRAs do not accept heat-stable formulations (that is, accept products for storage at 2-8°C).				
b) Data in the submission shows the product is heat stable (for example, store below 30°C), but WHO recommendations specify store in the refrigerator (that is, store at 2-8°C).				
c) Other NRAs have registered the product as a heat-stable product (that is, store below 30°C). Still, data in the submission shows the product is unstable at 30°C and should possibly be stored in the refrigerator (2-8°C).				
d) WHO recommendations consider the product as being a heat-stable product (that is, store below 30°C), but data in the submission shows the product is unstable at 30°C and should possibly be stored in the refrigerator (2-8°C).				
e) Data in the submission shows the product is heat stable (that is, store below 30°C), but prior decisions and products had store in the refrigerator (2-				

8°C).				
f) Data in the submission shows the product should be stored in the refrigerator (2-8°C), but prior decisions and products had the product as being heat-stable (that is, store below 30°C).				

Question 24:Where you have selected "Other" in any of the scenarios in Question 22, explain what would be done to resolve the conflict.

Your response has been submitted

If you have not done so already, please remember to complete the excel tool with information on the registered oxytocin products in your country.

Thank you

Your input to this assessment is valued.