

# REGULATORY GUIDANCE FOR ASSESSMENT AND MANAGEMENT OF APPLICATIONS

FOR MARKETING  
AUTHORIZATION  
OF OXYTOCIN





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**World Health  
Organization**



Regulatory guidance for assessment and management of applications for marketing authorization of oxytocin

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# ABBREVIATIONS

<b>API</b>	Active Pharmaceutical Ingredient
<b>EPI</b>	Expanded Programme on Immunization
<b>FPP</b>	Finished Pharmaceutical Product
<b>GMP</b>	Good Manufacturing Practice
<b>ICH</b>	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
<b>ISO</b>	International Organization for Standardization
<b>LMICs</b>	Low- And Middle-Income Countries
<b>MNCH</b>	Maternal, Newborn And Child Health
<b>PQS</b>	Performance, Quality And Safety
<b>TTI</b>	Time-Temperature Indicator
<b>UNFPA</b>	United Nations Population Fund
<b>UNICEF</b>	United Nations Children’s Fund
<b>USAID</b>	United States Agency for International Development
<b>WHO</b>	World Health Organization



# EXECUTIVE SUMMARY

Postpartum haemorrhage – excessive bleeding after childbirth – is a medical emergency that affects around five per cent of women who give birth each year. Left untreated, it can lead to anaemia, shock and death. Postpartum haemorrhage is the leading direct cause of maternal death in low- and middle-income countries (LMICs) (1).

Postpartum haemorrhage-related morbidity and deaths can be largely prevented by the use of prophylactic uterotonics during the third stage of labour, as well as timely and appropriate clinical care, including placental delivery and treatment of postpartum haemorrhage. Uterotonics such as oxytocin increase muscle contractions in the uterus, thereby compressing the blood vessels, and preventing and controlling bleeding (2).

Injectable oxytocin, given intravenously or intramuscularly, is recommended by the World Health Organization (WHO) as the first-line medicine for the prevention and treatment of postpartum haemorrhage. It is additionally used for the induction and augmentation of labour (3,4). It is included in the WHO Model List of Essential Medicines and is one of 13 priority life-

saving medicines listed by the UN Commission on Life-Saving Commodities for Women and Children. It is an inexpensive medicine that is widely manufactured and distributed (5).

Studies have identified high rates of substandard oxytocin in many LMICs, both in products that have achieved formal regulatory approval and those that have not. The primary causes for substandard oxytocin quality are considered to be poor-quality manufacturing and/or product degradation in the supply chain. Oxytocin is a drug that needs to be stored at 2°C–8°C (35°F–46°F) to ensure efficacy and potency, yet many products circulating in LMICs are not labelled or stored accordingly. Each of these factors points to critical responses needed from national medicines regulatory authorities, both on the quality of oxytocin manufacturer and dossier assessments, and on stronger regulatory oversight of oxytocin in markets.

The seriousness of this issue has compelled two recent publications from international agencies. In 2018, a consortium of the Reproductive Health Supplies Coalition, the United States Agency for International Development (USAID) and PATH

issued an advocacy messaging framework for oxytocin titled, ‘Buy quality oxytocin, keep it cold’ (6). It provided key messages aimed at national medicines regulatory authorities, public-sector procurement agents, supply chain managers, and maternal health programme leaders, highlighting actions they should each take to eliminate this problem. Subsequently, in 2019, WHO, the United Nations Children’s Fund (UNICEF) and United Nations Population Fund (UNFPA) released a joint statement on the appropriate storage and management of oxytocin, and the responsibilities of different actors nationally to accept only quality-assured oxytocin products in their market and then maintain them in the cold chain (7).

Pharmaceutical regulators are at the forefront of ensuring that only safe and effective medicines are authorized and available in the market. This document builds on the recommendations in the above publications and has been prepared

to specifically assist national medicines regulatory authorities to understand the nature and extent of oxytocin quality issues and to provide key technical information and quality requirements for oxytocin products in dossier assessments. Furthermore, this document also presents recommendations on other regulatory actions needed to ensure that only quality-assured oxytocin products are authorized and made available to women.

While the primary target audience is pharmaceutical regulators in national medicines regulatory authorities, the information may also assist manufacturers in the development of quality oxytocin. It may similarly assist procurers involved in identifying or prequalifying oxytocin products for procurement. Procurers may first wish to refer, however, to oxytocin guidance included in USAID’s ‘Manual for procurement and supply of quality-assured maternal, newborn and child health commodities’ (8).

# 1. OXYTOCIN QUALITY ISSUES

## 1.1. BACKGROUND

Studies confirm that there is a high prevalence of substandard oxytocin circulating in many low- and middle-income countries (LMICs). According to a 2016 literature review by the World Health Organization (WHO), over one third of the 559 samples from studies in LMICs were substandard. Possible causes for substandard oxytocin products include poor quality of manufacturing, unsuitable storage, labelling and shelf-life, and inappropriate transport and storage conditions throughout the supply chain (9). Due to its unstable nature, if an oxytocin product is not of sufficient quality when produced, or if it is not managed in the cold chain, the medicine will rapidly degrade and become ineffective, thereby risking women's lives.

Noting this concern, in 2019, WHO, the United Nations Children's Fund (UNICEF) and the United Nations Population Fund (UNFPA) issued a joint statement underscoring the importance of the availability of quality-assured oxytocin

(7). It recommended three urgent actions to ensure the effective management of and access to good-quality oxytocin:

1. Label oxytocin to clearly indicate storage and transport requirements at 2°C–8°C (35°F–46°F);
2. Ensure that oxytocin is managed in a cold chain of 2°C–8°C (35°F–46°F) for distribution and storage;
3. Procure oxytocin that meets the quality requirements established by WHO or a regulatory authority recognized by WHO.

## 1.2. CONSEQUENCES OF SUBSTANDARD OXYTOCIN

The use of substandard oxytocin carries risks for the mother, her infant and other family members, as well as for the health-care system of a country. Table 1 outlines the harmful effects that problems with the quality of oxytocin may cause to a mother's health (10).

*Table 1. Potential medical consequences of oxytocin quality problems*

QUALITY PROBLEM	POTENTIAL EFFECT
Excessively high content of active pharmaceutical ingredient (API) (over 110%)	Excessive oxytocin can cause side-effects such as low blood pressure and/or contractions that are too strong.  This is often due to substandard manufacturing processes. Although rare, some manufacturers compensate for the potential degradation of oxytocin by including unjustified overage of active ingredient.
Inadequate API content (less than 90%)	Too little oxytocin can result in failure of the uterus to contract, leading to continued bleeding, complications and potential death.  When the uterus fails to contract, health-care providers need to administer additional uterotonics, often using several doses or combinations of drugs. The woman may also need fluids and blood transfusions, and surgical interventions such as uterine artery ligation, sutures or a hysterectomy.
Contains contaminants/impurities (foreign substances such as bacteria, other chemicals, unidentifiable compounds, solid particles, etc.)	Medicines containing anything other than what they are intended to contain can cause serious and sometimes fatal consequences, including allergic reactions and infections that may result in death.  Poor-quality oxytocin may contain unidentified foreign substances and could produce toxic substances on degradation.
Non-sterile injectables	Unsterile injectable medicines can cause serious infections and sometimes death.

While the financial cost of poor-quality oxytocin to a woman’s family and the health-care system has not been reliably estimated, two studies do provide some insight into this serious consideration. A recent study in four LMICs analysing the additional cost of hospital care for women who experience postpartum haemorrhage against those who do not found an increase in total hospital costs of up to 4.1 times (11). A qualitative study concluded (12):

- The loss of a mother harms her surviving family members, and her children’s health, education and future opportunities;
- Maternal death is linked to high neonatal mortality: of the 59 maternal deaths in the study, only 15 babies survived the first 60 days of life;
- The cost of fatal pregnancy and childbirth complications is a heavy economic burden;
- When a woman dies, her funeral costs can be a crippling hardship for her family;

- The sudden loss of a productive woman disrupts the family’s economy and its daily life.

### **1.3. EVIDENCE OF SUBSTANDARD OXYTOCIN IN LMICs**

Many studies have raised the issue of poor-quality oxytocin at the point of sale and use in LMICs, particularly in Africa and Asia.

Note that all studies have focused primarily on the content of the active pharmaceutical ingredient (API content, or assay). Many studies have additionally included tests for sterility, but fewer have tested other key quality parameters such as pH, related substances, particulate matter and endotoxins. Studies may therefore underestimate the prevalence of products not meeting acceptable international quality standards.

An extensive survey was organized by the WHO prequalification team in cooperation with the national medicines regulatory authorities of 10 countries in Africa, Asia and South America, to assess the quality of 13 life-saving medicines available at the first level of the distribution channel. Of the 13 products tested, the highest proportion of non-compliant samples was found for oxytocin injection (64 per cent). Samples of oxytocin injection (22 batches) produced by 15 manufacturers were assayed using the oxytocin injection monograph specified in The International Pharmacopoeia. Among the 14 non-compliant batches, the oxytocin API content was below the acceptance limit in seven samples. In two batches, it was as low as 52 per cent and 78 per cent of the labelled content. In six batches, the content of related substances was above the limit, suggesting the degradation of oxytocin and the presence of degradation products.

Figure 1 demonstrates the non-homogeneity of ampoules found in a single batch of product identified to be extremely substandard. Notably, 18 of the 22 batches sampled were

products registered by the relevant national medicines regulatory authority, three products were procured through central government procurement, and one product was a donation received into the government central store. The adverse findings of the study highlight a need for improved regulatory control of oxytocin products, both formally through the national registration channel as well as through government procurement mechanisms (13).

A systematic review of literature by WHO in 2016 consolidated all of the evidence to date on the quality of oxytocin sampled from public and private supply chains in LMICs. It found that, across all of the studies included in the review, the median prevalence of oxytocin samples that did not pass quality testing was 46 per cent, and the median prevalence of oxytocin with inadequate API content was 36 per cent. The proportion of ampoules failing international specifications was 58 per cent in Africa and 22 per cent in Asia. All 14 samples from the two Latin American countries included in the study passed API content. Among other limitations, the review acknowledged both the possibility of

*Figure 1. Non-homogeneity of ampoules in a single batch of oxytocin products*



studies with favourable results being excluded due to difficulty getting published (publication bias), but also the more likely concern that surveys with very unfavourable results (high rates of failed samples) had not been made publicly available by national authorities (9).

Since the publication of the systematic review, several field surveys have reinforced the concern about a high prevalence of substandard products in many LMICs. These surveys are summarized in Table 2.

Table 2. Field studies on oxytocin quality

STUDY	SAMPLE SIZE	REGULATORY AUTHORITY REGISTRATION	STORAGE CONDITIONS	ANALYTICAL TESTS	RESULTS
Ministry of Health and Family Welfare, 2017; India (14)	58 samples (unknown quantity of units per sample)	Not reported	Not reported	Assay, others*	41% failed assay (<90% content) *Results of any additional tests carried out were not reported
Lambert et al., 2018; Democratic Republic of the Congo (15)	15 samples (6–20 ampoules per sample)	1 product registered; 3 unregistered; 1 unknown status	Ambient conditions	Assay, impurities, sterility	80% failed assay (range 48% to 105%) All samples tested passed sterility All contained unknown impurity No samples were refrigerated or labelled for refrigeration
Anyakora et al., 2018; Nigeria (16)	159 samples (unknown quantity of units per sample)	All products registered	Various conditions (measured)	Assay, particulate matter	74% failed assay (range 0% to 164%) All samples passed particulate matter and labelling Few samples were refrigerated
Lambert et al., 2019; Ethiopia (17)	45 samples (9–25 ampoules per sample)	1 product registered; 2 unregistered	95% of samples in refrigerator	Assay, impurities, sterility, endotoxin	4% failed assay (range 78% to 109%) All samples that passed assay also passed any additional tests performed 2 failed samples collected from rural facilities in remote region with a very hot climate
Hagen et al., 2020; Malawi (18)	65 samples (8–20 ampoules per sample)	3 products registered; 6 unregistered	Various conditions (measured)	Assay, pH	11% failed assay (range 82% to 105%) All samples passed pH

These findings paint a worrying picture about the quality of oxytocin products being given to women in emergency medical care in LMICs and the adverse outcomes that may result. National regulators must act urgently to better assure the safety and efficacy of products in their countries.

## 1.4. CAUSES OF SUBSTANDARD OXYTOCIN

### 1.4.1. Manufacturing

Oxytocin is a relatively inexpensive generic medicine no longer subject to patent protection. It is manufactured and distributed widely, with nearly 300 different products around the world (5). Two oxytocin brand names are broadly recognized: Syntocinon, which is marketed by

Novartis, and Pitocin, which is marketed by Pfizer or its partners. There are multiple generic oxytocin products in almost all countries that have active pharmaceutical manufacturing sectors in sterile injectables, including Argentina, Bangladesh, China, India, Indonesia and Pakistan. India alone has over 100 different manufacturers registered to produce the medicine.

The first oxytocin product was prequalified by the WHO prequalification programme in April 2015. As of July 2020, only three oxytocin products from three manufacturers are prequalified, as listed in Table 3. The current status can be found on the WHO prequalification programme website at <https://extranet.who.int/prequal/content/prequalified-lists/medicines>.

Table 3. Oxytocin injections prequalified by WHO\*

WHO REFERENCE NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DATE PREQUALIFIED	SHELF LIFE	STORAGE CONDITION
RH050	PT Sanbe Farma, Indonesia	Finished pharmaceutical product manufacturing site: PT Sanbe Farma, Sterile Preparation Plant, Unit 3, Jl. Industri Cimarene No. 8, Desa Cimareme, Kecamatan Ngamprah, Kabupaten Bandung Barat, 40553, Indonesia Active pharmaceutical ingredient manufacturing site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia	30 June 2017	18 months	Store in a refrigerator (2°C–8°C), do not freeze, protect from light
RH079	JSC Grindeks, Latvia	Finished pharmaceutical product manufacturing site: HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia Active pharmaceutical ingredient manufacturing site: JSC Grindeks, 53 Krustpils Street, Riga, 1057, Latvia	14 October 2019	36 months	Store in a refrigerator (2°C–8°C), do not freeze
RH083	Steril-Gene Life Sciences (P) Ltd, India	Finished pharmaceutical product manufacturing site: Steril-Gene Life Sciences (P) Ltd., 45, Mangalam Main Road, Mangalam Village, Villianur Commune, Puducherry, 605 110, India	14 October 2019	24 months	Store in a refrigerator (2°C–8°C), do not freeze, protect from light

\* All prequalified oxytocin formulations are solutions for injection, packaged in 10 IU/1mL, type 1 glass ampoules

Because there are so many manufacturers of the drug, and until recently few WHO prequalified products, it has historically been challenging for regulators and procurement agencies in LMICs to identify quality products. Moreover, oxytocin quality studies have identified some unregistered or unlicensed medicines in LMICs that might have bypassed routine quality assessments.

For manufacturers, the low price per ampoule of oxytocin and the large number of manufacturers creates a price-sensitive market. Some manufacturers may compromise the quality of the product to keep prices low and boost sales. Good quality comes at a price, either in equipment costs, better ingredients or the higher process cost of quality assurance (19,20). The lack of quality may be the result of a variety of factors, including:

- use of substandard or incorrect APIs or excipients, and/or their inadequate control or storage
- poor control of environmental conditions during the manufacturing
- manufacturing processes that cause contamination or do not adequately ensure sterility
- inadequate packaging design or quality for API and/or finished pharmaceutical product (FPP).

### *Substandard or incorrect APIs and/or excipients and/or their inadequate control or storage*

In some markets, national regulatory authorities do not fully assess API quality, or do not require or enforce API quality testing by manufacturers of the FPPs. Without a process in place to assure API quality, the resulting FPP may be of poor quality. API quality can often be compromised by the presence of chemical impurities arising from toxic and banned solvents and reagents used in synthesis because they are inexpensive. Impurities can alter medication properties

or be toxic. Some FPP manufacturers rely only on certificates of analysis from the API manufacturers, which are often unverified, and focus solely on quality control tests of the FPPs. Any quality defect of the API is transferred to the FPP during production. Hence, by not testing the quality of the API, significant quality attributes of the FPP can be overlooked or affected. Finally, oxytocin API requires refrigeration (at 2°C–8°C) during transportation and storage. This is an important issue, particularly in tropical settings, where the controls in place may be insufficient to ensure the proper transportation and storage conditions, leading to API degradation (21).

Excipients can potentially affect the product's performance, stability and bioavailability, and ultimately its quality, efficacy and safety. Medicines that are poorly formulated can become unstable and degrade. This compromises their shelf life. Degradation processes are often accelerated at high temperatures and high humidity, causing products to lose efficacy over time. Poorly formulated medicines often fail to deliver the right amount of API to the right part of the body at the right time, resulting in reduced therapeutic effectiveness. For oxytocin, excipients should be properly selected to ensure that they meet acceptable standards and also to ensure the appropriate pH for optimal formulation stability (21).

*Section 2 provides further technical information on selection of the A*

### *Poor control of environmental conditions during the manufacturing*

Oxytocin can be degraded by high temperature, high relative humidity and light exposure. Therefore, appropriate environmental conditions and process temperature control are necessary. Achieving this at the manufacturing facility requires proper infrastructure that is not always available in production and storage areas.



*Section 2 provides further technical information on environmental conditions and monitoring.*

### ***Manufacturing processes that cause contamination or do not adequately ensure sterility***

Substandard medicines are also caused by contamination during the manufacturing process. When good manufacturing practice (GMP) is not followed, cross-contamination can occur among products manufactured at the same facility. Cross-contamination happens when equipment is not properly cleaned before the changeover of products, there is a lack of proper air-handling systems to prevent the movement of dust particles from one medicine in production to the next, when contaminated water is used during manufacturing processes (leading to high microbial burdens), or where there are unhygienic practices. Drug contamination can easily go unnoticed since quality-control tests may be designed to assess only the levels of expected impurities in the FPP (21).

The selection of an unsuitable sterilization method such as heat sterilization can also affect the quality of oxytocin (it will degrade if exposed to high process temperatures). In addition, unsuitable aseptic practices or lack of controls during filtration, filling and sealing of the ampoules/vials can result in a contaminated product.

*Section 2 provides further technical information on product sterilization/sterile filtration*

### ***Inadequate packaging design or quality for API and/or FPP***

The stability of a formulation in a variety of storage conditions is also an important issue, particularly in Climatic Zone IV. Drug stability can be influenced by packaging, and appropriate packaging is particularly important in conditions such as high humidity, heat or strong

light. Unfortunately, issues such as packaging are not as tightly controlled as API content, and the packaging used for generic products in particular may be less able to withstand certain storage conditions.

Similarly, the transportation, packaging and storage of the API prior to FPP manufacture is a critical factor in the quality of the FPP.

*Section 2 provides further technical information on packaging and presentation.*

When adhered to, GMP standards ensure the consistent manufacture of products free of contamination. They help to ensure that products are consistently produced and controlled according to uniform quality standards and are designed to minimize the risks involved in pharmaceutical production.

When considering regulatory applications for oxytocin products, it is critical that GMP compliance has been carefully assessed by an adequately stringent inspection body. Due to the exceptionally high risks to quality for this life-saving medicine, WHO, UNICEF and UNFPA recommend that, where feasible, oxytocin should be authorized and procured from sources that are either WHO-prequalified or approved by a recognized regulatory authority (7). If these sources are not available, at a minimum, the product should be manufactured in compliance with GMP as well as internationally recognized pharmacopoeial standards to be considered for risk assessment and potential temporary procurement while the manufacturer pursues prequalification by WHO or approval by a recognized regulatory authority.

#### **1.4.2. Temperature-related degradation during transport and storage**

Oxytocin has been shown to be a heat-sensitive product that requires cold-chain storage to prevent degradation and loss of potency. While short excursions outside of the temperature range of 2°C–8°C (35°F–46°F) may

not compromise the quality of the product, longer-term storage and distribution outside these temperatures are likely to result in product degradation and ineffective treatment (22). Knowledge of this issue is not widespread among health-care providers, policy-makers and supply chain experts in some LMICs (23).

Numerous studies have demonstrated that oxytocin formulations show negligible degradation under refrigerated conditions,

but degrade rapidly at ambient temperatures (22,24–27). In a simulation study conducted by WHO in collaboration with IDA Foundation, two batches of three brands of oxytocin ampoules were stored at a range of temperatures, and samples were assayed for oxytocin content over two years (22). Table 4 and Figure 2 show the study results and the subsequent oxytocin shelf-life guidelines suggested by WHO and the IDA Foundation.

*Table 4. Oxytocin shelf-life guidelines drawn from study findings*

TEMPERATURE	AVERAGE LOSS OF POTENCY	SHELF-LIFE RECOMMENDATIONS
2°C–8°C	No loss at 1 year	3 years
25°C	1% loss in 1 month 3–7% loss per year	1 year
30°C	9–19% loss per year	6 months
40°C	6% loss per month	Maximum 1 week

The results of recent field studies have reaffirmed the correlation between ambient storage conditions and oxytocin degradation (28). A 2018 study in the Democratic Republic of Congo, which found 80 per cent of samples failed API content, observed that none of the products was labelled for refrigerated storage, nor was any refrigerated (15). In Nigeria, the large majority of samples were not refrigerated in a 2018 study observing that 74 per cent of samples failed API content (16). Conversely, a more positive study finding was seen in Ethiopia, a country where the awareness of oxytocin’s temperature sensitivity has been measured to be high among health-care workers (23). Of the 45 samples tested in the study, only two samples (4 per cent) failed API content – both were found in rural facilities in the same remote, poorly resourced region with a very hot climate. Notably, all samples in the study were labelled for storage at 2°C–8°C, and about 95 per cent of samples had been stored in compliance (17).

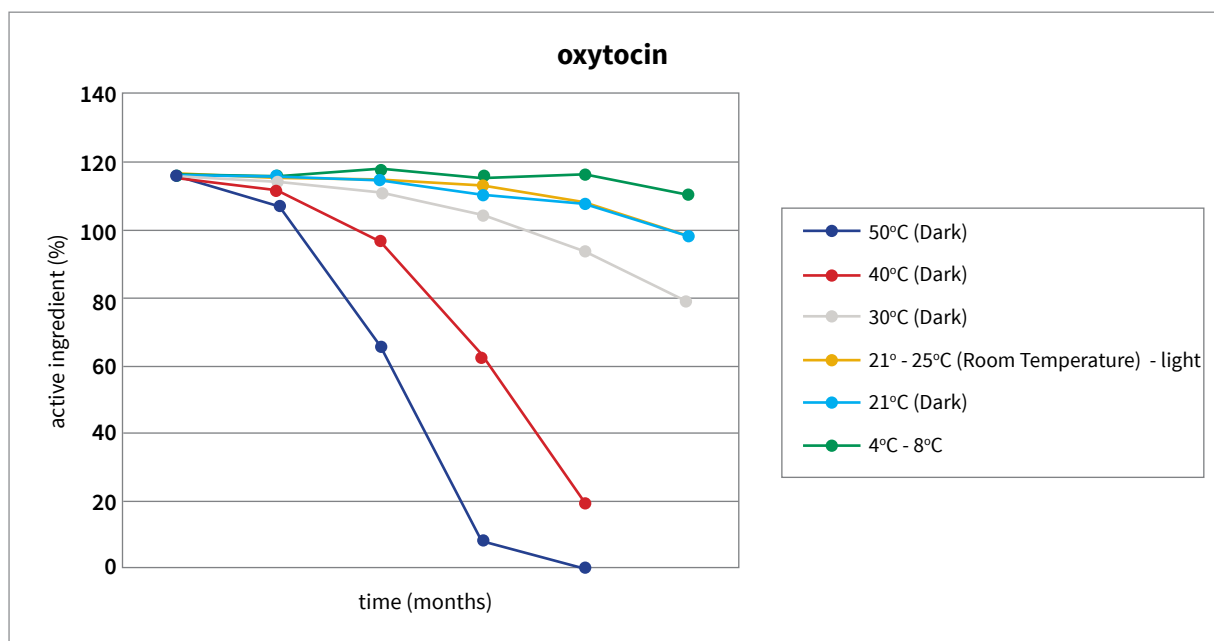
This stability profile has been seen across different formulations, whether labelled and marketed for storage at 2°C–8°C or at ambient temperatures. A recent simulation study by Monash University in collaboration with the UNFPA, under a variety of conditions, compared the stability of several oxytocin products formulated and labelled for storage below 25°C with those labelled for refrigerated storage (27). Multiple batches of three products labelled for storage at 2°C–8°C and two products labelled for storage at below 25°C were included in the study. All products otherwise met UNFPA quality standards. Accelerated studies of stability and temperature cycling (alternating between 30°C, 40°C and 50°C for 30 days and refrigerated temperatures for 15 days) were performed over four months. The results found that the products designated for storage at below 25°C quickly degraded in higher temperatures in the same way as those labelled for refrigerated storage and, in one example, demonstrated

poorer stability characteristics. These results raise serious concern for the stability of products present in LMIC markets labelled for storage at below 25°C, below 30°C or similar.

These controlled laboratory stability studies are complemented by observational studies tracking supply-chain temperatures found in LMICs. Hogerzeil and others showed the maximum temperature to which products were exposed during the shipment of essential commodities from Copenhagen to Lagos,

Kampala and Bangkok was 33.6°C, 42.4°C and 37.5°C, respectively (29). In a recent observational study in Ghana, by WHO, temperatures along the oxytocin supply chain, from manufacturer to points of use in Ghana, ranged between -9.9°C and 30.1°C (30). In a recent study in Malawi, Hagen and others observed mean kinetic temperatures in the storage areas of non-refrigerated oxytocin of 21.4°C to 31.0°C, with single temperature readings up to 40.1°C (18).

Figure 2. Stability of oxytocin injections stored at different temperatures for two years



Reproduced courtesy of Thakral et al. (28)

Countries with tropical climates, where daily temperatures frequently exceed 30°C (86°F), are at particular risk for oxytocin failures if the formulation is not maintained in an appropriate cold chain. This would apply to the majority of LMICs, which are classified as either Climatic Zone IVa or IVb by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Resource limitations in LMIC supply chains mean that medicines not controlled in the cold chain may be subject to such events due to long customs

clearance delays, or storage in warehouses, health centres and pharmacies without temperature control or consistent electricity supply.

As a result, irrespective of manufacturer labelling, WHO, UNICEF and UNFPA recommend that supply chain managers ensure that all oxytocin products are maintained at 2°C–8°C during transportation and storage (7). National medicines regulators should provide oversight of oxytocin cold-chain compliance in their

market. They are compelled to support and enforce these requirements in the appropriate labelling and marketing of registered products. Similarly, the WHO prequalification programme now accepts applications for oxytocin products labelled for storage only at 2°C–8°C, with no additional statement for short-term excursions outside this range (31).

One option that has been explored to determine whether oxytocin available at the point of care has been exposed to unacceptable temperature excursions is the use of time-temperature indicators (TTIs) on the product label, similar to the vaccine vial monitors used in immunization programmes. Oxytocin formulations incorporating a TTI have previously been developed in the Uniject device, although the added complexity to manufacturing comes at significantly higher cost, and such products have not become widely available in LMICs. Work continues to explore the integration of TTIs into oxytocin products at prices that are commercially viable in LMICs.

Note that in addition to heat, other potential determinants of oxytocin degradation are pH and light exposure, although they would appear less critical (32,33). The ideal pH range for oxytocin is considered to be between pH 3 and pH 5, and field survey studies analysing pH have not identified samples outside of this specification (13,18,34). The effect of light exposure on oxytocin is inconclusive. While the above-mentioned study from Hogerzeil and others (22) concluded that light exposure had no destabilizing effect, a study performed by Mozziconacci and Schöneich in 2012 (33) indicated that oxytocin can be degraded by light. (See Figure 2; it should be noted that the study by Hogerzeil and others did not measure light exposure in compliance with ICH Q1B (35), and so should not be the basis for waiving the labelling requirement, “protect from light”.) According to the Mozziconacci and Schöneich

study, oxytocin was sensitive to ultraviolet light at pH 4–5 and pH 7–8. As a precaution, exposure to light should be minimized through appropriate formulation, packaging and storage of both the API and the FPP, and all formulations should be labelled “protect from light” unless manufacturers provide appropriate stability data.

*Section 2 provides guidance for national authorities to ensure dossiers meet suitable criteria with respect to temperature control and stability, including the requirements of TTIs where they are used.*

### 1.4.3. Inappropriate storage recommendations and shelf life

While it is generally accepted that oxytocin products quickly degrade outside of refrigerated conditions, there is a lack of clarity in international reference pharmacopoeial monographs. The British Pharmacopoeia and United States Pharmacopoeia monographs for oxytocin injection are not prescriptive about storage temperature. To meet the requirements of LMICs, WHO and The International Pharmacopoeia have clarified that oxytocin injection should always be formulated, labelled and marketed for storage at 2°C – 8°C.

It is the responsibility, however, of a manufacturer to demonstrate the stability of their products in their product development and dossier applications. The labelled storage conditions for oxytocin products available in LMICs have proven to be very diverse. Table 5 summarizes the labelled storage conditions and the corresponding shelf lives for products sampled in the above-mentioned 10-country survey conducted by WHO and national medicines regulatory authorities. The survey included products manufactured in six countries by 15 manufacturers (13).

Table 5. Recommended storage and shelf life of products manufactured in different countries (13)

SERIAL NUMBER	MANUFACTURER	COUNTRY OF MANUFACTURE	COUNTRY OF COLLECTION	RECOMMENDED STORAGE ON LABEL	SHELF LIFE ON LABEL
1	Zhejiang Tianfeng Pharmaceutical	China	Burkina Faso, Uganda	Store in cool and dark place	3 years
2	Zhejiang Ruixin Pharmaceutical Co Ltd	China	Uganda	Secondary packaging not available	3 years
3	North China Pharmaceutical Co Ltd (NCPC)	China	Madagascar	Keep in cold, dry and dark place	3 years
4	Ningbo Dahongying Pharmaceutical Co Ltd	China	Uganda	Below 25°C, protect from light	3 years
5	Vital Healthcare Pvt Ltd	India	United Republic of Tanzania	8°C–25°C, do not freeze	2 years
6	Nitin Lifesciences Ltd	India	Tajikistan	Below 25°C, do not freeze, protect from light	2 years
7	Hindustan Chemicals & Pharmaceuticals	India	Nepal	Do not freeze	2 years
8	Umedica Laboratories Pvt Ltd	India	Kenya, Nepal	Not exceeding 30°C	3 years
9	Tablets (India) Ltd	India	Viet Nam	Not exceeding 30°C, do not freeze	2 years
10	Kwality Pharmaceutical Ltd	India	Nigeria	2°C–8°C, protect from light and heat	3 years
11	Akums Drugs & Pharmaceuticals Ltd	India	Nepal	Store in a cold and dark place, do not freeze	2 years
12	Rotexmedica GmbH Arzneimittelwerk	Germany	Burkina Faso, United Republic of Tanzania, Viet Nam	2°C–8°C, do not freeze	3 years
13	Biologici Italia Laboratories Srl	Italy	Zimbabwe	Below 25°C, protect from light	2 years
14	Bryntsalov – A ZAO	Russian Federation	Tajikistan	8°C–20°C, protect from light	3 years
15	Gedeon Richter Plc	Hungary	Tajikistan	2°C–15°C, protect from light	3 years

More recent field surveys confirm the high prevalence in LMICs of products recommending storage “below 25°C”, “below 30°C”, or providing ambiguous instructions such as “store at room temperature” (15). In a 2020 study in Malawi, 23 of 65 samples (35 per cent) were labelled for storage at 2°C–8°C, whereas 42 (65 per cent) were labelled for storage below 25°C or below 30°C. Notably, none of the samples labelled for refrigerated storage was found to be out of specification. In contrast, seven of the 42 samples labelled for storage below 25°C or below 30°C showed insufficient API content (18). While some manufacturer labelling continues to indicate that oxytocin is stable for long periods at ambient temperatures, the data supporting these claims are not available. Such labelling for oxytocin products is unsuitable in many LMICs,

where hot climates and resource limitations will result in frequent exposure to temperatures above 30°C if products are stored under ambient conditions.

Some oxytocin products authorized in highly regulated countries designated as ICH Climatic Zones I and II, such as in those authorized in the European Union and the United States of America, are labelled for storage at up to 25°C (77°F). These products cannot be considered suitable for use in LMICs classified as Climatic Zones III or IV.

*Section 2 details technical guidance on the specifications and conditions, including the temperature sensitivity of oxytocin, required to demonstrate stability.*

## 2. TECHNICAL INFORMATION AND REGULATORY RECOMMENDATIONS FOR OXYTOCIN INJECTION

### 2.1. BACKGROUND

This section provides an overview of the chemical and physical characteristics of oxytocin, with a view to identifying appropriate manufacturing processes and controls required to produce high-quality oxytocin formulations. Also detailed is information on other critical factors, such as packaging and transportation/storage, required to make effective oxytocin products available to all users.

In association with the technical details stated, regulatory recommendations and relevant dossier evaluation details deemed critical to the assessment of oxytocin products have been placed in this section as 'Notes for regulators' following the relevant technical information. This is intended to provide guidance to national medicines regulatory authorities assessing oxytocin products, with the objective of ensuring approval of only high-quality oxytocin products. Suitable scientific justification should be applied to submissions containing supporting data that differ from those detailed within this document.

It is not intended as a stand-alone guide and should be used in conjunction with equivalent national and international guidelines related to quality, and safety and efficacy.

### 2.2. GENERAL INFORMATION, STABILITY AND DEGRADATION

#### Name of The Medicinal Product

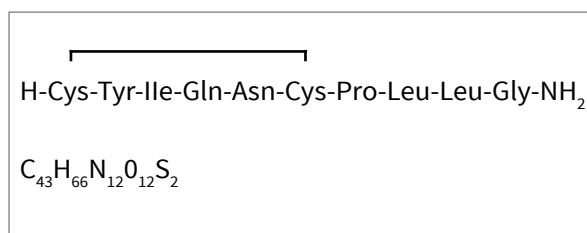
Oxytocin injection

#### Chemical name

Oxytocin (L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide).

Oxytocin is a synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. Being wholly synthetic, it does not contain vasopressin and has a constant and reliable effect.

## Chemical structure



The sequence of oxytocin is cysteine–tyrosine–isoleucine–glutamine–asparagine–cysteine–proline–leucine–glycinamide, with a disulfide bridge between the first and sixth cysteines, forming a six-amino-acid ring with a tripeptide tail.

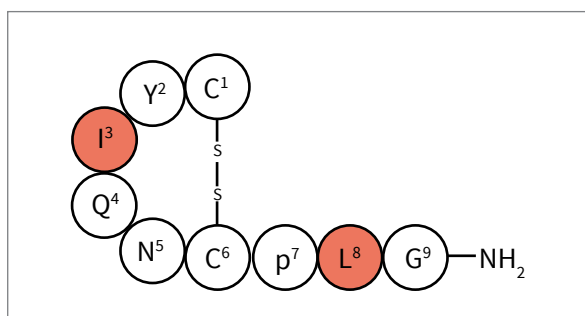


Figure 3. Oxytocin structure

Letters identify the amino acids, numbers their positions in the sequence of neuropeptides (36)

According to Hawe and others (2009), asparagine (N5) and tyrosine (Y2) “are the key moieties required for proper function at the active site of the uterine receptor” and isoleucine (I3), glutamine (Q4), proline (P7) and leucine (L8) “are important for receptor binding. Any changes in the structure caused by chemical or physical instabilities can lead to loss of affinity to the receptor and/or altered biological activity” (32).

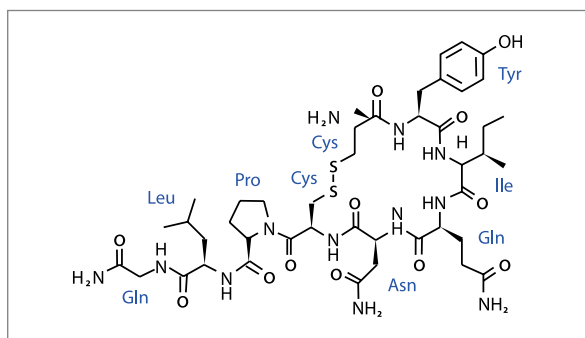


Figure 4. Oxytocin molecular structure

## Pharmaceutical form

Sterile solution for injection.  
A clear, colourless solution.

## Stability concerns for oxytocin formulations

The available literature related to oxytocin stability highlights the thermal instability of the product. The particular concerns are:

- The rate of degradation increases as temperature exposure increases (length of exposure and temperature);
- The degradation mechanisms of oxytocin depend on the formulation pH;
- The combination of an initial photo stress and a subsequent heat stress can yield products significantly different compared with those observed under heat stress only.

Product degradation can lead to a reduced API level and hence compromised performance. According to Thakral and others (2018), “Concerns are frequently raised about the challenge of maintaining the effectiveness of oxytocin for [postpartum haemorrhage] prevention in tropical settings when refrigerated storage conditions cannot be assured. When oxytocin is exposed to high temperatures for extended periods of time, the effective dose can drop below the prescribed industry standard of 90 to 110 per cent of the labelled claim. This can be a critical constraint in LMICs, where consistent and reliable cold-storage capability is often lacking” (28).

Oxytocin could be susceptible to degradation via deamidation, oxidation or thiol exchange. The degradation rate and mechanism depend on the formulation pH, temperature, relative humidity and light.

## pH

The ideal pH range for oxytocin is pH 3 to pH 5, with the most stable formulation being pH 4.5. In strongly acidic solutions, the peptide linkage



undergoes hydrolysis. Under neutral and weakly alkaline conditions, dimeric and polymeric compounds are formed by conversion of the intramolecular disulfide bridges of two or more oxytocin monomers to intermolecular bridges (disulfide interchange) (28,33).

## Temperature

The API, bulk and finished product should not be subjected to high temperatures (ideally it should be kept within 2°C–8°C). Should the API be subjected to temperatures out of this range under any circumstance – such as during weighing or sampling – the exposure time should be as short as possible.

Both chemical degradation and aggregation are the dominant degradation mechanisms of oxytocin at elevated temperatures. The degradation mechanisms depend on the formulation pH. Various deamidated oxytocin molecules were identified at pH 2 and pH 9. At pH 4.5, pH 7 and pH 9, the formation of tri- and tetrasulfide-containing monomeric oxytocin, different oxytocin dimers and larger aggregates was identified (32).

A further factor affecting some oxytocin products is the inclusion of an excipient, namely chlorobutanol, which is also susceptible to high temperatures, and its degradation further accelerates oxytocin loss. The mechanism of oxytocin degradation caused by the combination of chlorobutanol and high temperatures is further described in the ‘Notes for regulators’ later in this document, under the section ‘Specific recommendations for the excipients – chlorobutanol’.

## Light

The available information described in the pharmacopoeias and literature about the light-destabilizing effect on oxytocin is not homogeneous. While the United States Pharmacopoeia does not mention any requirement about light protection, the current guidelines in The International Pharmacopoeia and European Pharmacopoeia recommend

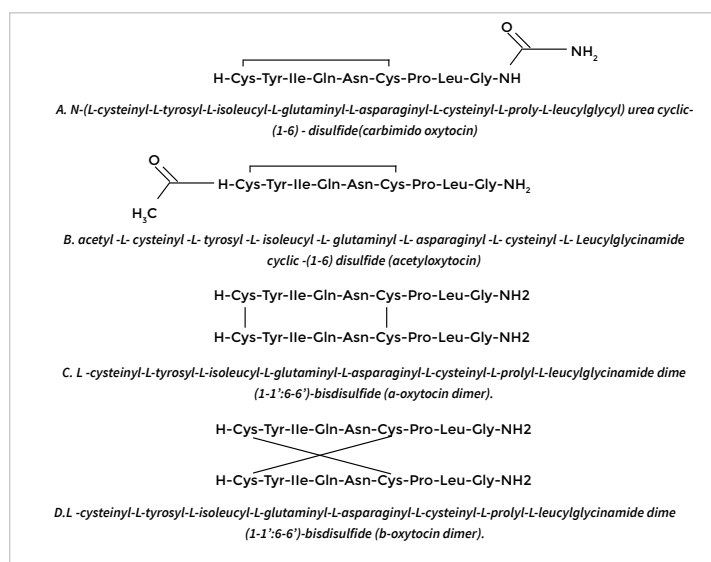
protecting oxytocin from light exposure.

As previously mentioned, the literature also provides different conclusions about degradation by light. According to Mozziconacci and Schöneich (2012), oxytocin in the presence of argonium (ArH<sup>+</sup>) or air can be converted into its thioether and dithiohemiacetal derivatives after ultraviolet light exposure (wavelength equal to 253.7 nm and wavelength greater than 290 nm). The study has demonstrated that under an inert atmosphere, the combination of light and heat stress leads to the transformation of the disulfide bond of oxytocin into a thioether and, under air, subsequent heat stress leads to the formation of non-reducible cross-links (33). In contrast, the study from Hogerzeil and others (1993) concluded that light exposure had no destabilizing effect (22). The study did not, however, measure light exposure in compliance with ICH Q1B (35), and so should not be the basis for waiving the labelling requirement to protect from light.

## Degradation products

Degradation is mainly the result of chemical instability at the disulfide bond, leading to dimerization and formation of sulfur-related impurities such as trisulfide, tetrasulfide and trimers. Oxytocin instability is therefore directly linked to its molecular structure.

The following impurities are described in The International Pharmacopoeia:



## NOTES FOR REGULATORS

Across recognized pharmacopoeias there is divergence between oxytocin API and FPP storage conditions:

- The International Pharmacopoeia states “protected from light, at a temperature of 2°C to 8°C” for oxytocin API and “kept protected from light and, unless otherwise indicated on the label, stored at a temperature between 2°C and 8°C” for oxytocin FPP.
- European Pharmacopoeia states “2°C–8°C, protected from light” for oxytocin API.
- Japanese Pharmacopoeia states “In a cold place, and avoid freezing”, a cold place being defined as having a temperature of 1°C–15°C for oxytocin FPP.
- United States Pharmacopoeia states “in a refrigerator” for oxytocin API, but does not specify a storage temperature for oxytocin FPP.
- British Pharmacopoeia and Indian Pharmacopoeia do not specify a storage temperature for oxytocin FPP.

Oxytocin is susceptible to degradation by heat. Careful storage at all stages of manufacture and throughout the supply chain is therefore needed. The effects of freezing temperatures have been observed in one study in which oxytocin was found to tolerate freeze–thaw cycles for up to seven days (37). However, data on long-term exposure to freezing temperatures are lacking, and freezing oxytocin should therefore be avoided.

Note that stability is dependent on formulation and packaging. That is, even small differences in the formulation and/or packaging may result in significant differences in stability. For example, a study on one product that shows stability under freezing conditions does not provide proof of stability at such conditions for another product.

WHO, UNICEF and UNFPA do not recommend that excursions exceeding the 2°C–8°C temperature range are included on oxytocin product labels (7).

The literature data on oxytocin stability with light are not conclusive. However, when the officially recognized pharmacopoeias (e.g., British Pharmacopoeia, European Pharmacopoeia, The International Pharmacopoeia, Japanese Pharmacopoeia and United States Pharmacopoeia) state that oxytocin as API or FPP should be protected from light, the regulator should insist that “protect from light” is included in the labelling and container-closure system’s design, unless the manufacturer can provide data from the photostability study meeting the ICH Q1B requirements (35) or the packaging is demonstrated to be light-protective.

It is therefore recommended that all oxytocin products should be labelled:  
“Store in a refrigerator (2°C to 8°C), do not freeze, protect from light.”

Statements on short-term excursions should not be included on oxytocin product labels. For oxytocin products being registered through Reference Regulatory Authority recognition procedures, it is vital to consider if the submitted stability data adequately support storage at 2°C–8°C in the proposed product market.

Oxytocin products approved by Reference Regulatory Authorities with storage conditions ranging up to 25°C should not be considered suitable for countries within WHO Climatic Zones III, IVb and IVb, all of which require long-term storage conditions of 30°C with varying percentages of relative humidity.

Stability conditions for WHO Member States can be assessed at the following web page:

[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/StabilityConditions/UpdatedAugust2018.pdf](https://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditions/UpdatedAugust2018.pdf)

Furthermore, ICH Q1A (38) requires products with proposed long-term storage at 25°C to undergo testing at accelerated conditions

of 40°C for a minimum of six months. There are no available data to demonstrate that oxytocin products can meet this requirement; therefore, any submitted stability data should be reviewed carefully.

## 2.3. CRITICAL FACTORS AFFECTING OXYTOCIN PRODUCTION

Critical factors that should be considered during the product development and manufacturing stages for oxytocin include:

- selection of the supplier of the API
- formulation and selection of the excipients
- production environment (temperature and appropriate aseptic conditions).

### 2.3.1. Selection of the API

Oxytocin is a nonapeptide hormone that causes the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary gland. It is prepared by synthesis.

Oxytocin is hygroscopic. It should be kept in an airtight container, protected from light, at a temperature of 2°C–8°C or, if sterile, in a sterile, airtight, tamper-evident container.

### Special requirements for sterile API

When oxytocin injection is manufactured by aseptic technique for the whole process, the sterile grade of oxytocin API is required. If it is to be manufactured by sterile filtration of the bulk solution followed by aseptic filling, the non-sterile grade can be used but there should be controls on the total viable count and bacterial endotoxin.

## NOTES FOR REGULATORS

Where sterilizing filters are employed to render the oxytocin API sterile, the compatibility of the filters should be demonstrated. Results from a recent media-fill study should also be provided if aseptic processing is the method of choice.

Where the oxytocin API is sterilized by irradiation, the bioburden prior to irradiation should be controlled (as for API sterilized by filtration). The validation and control of the irradiation process should take into account the recommendations in ISO 11137 (sterilization of health-care products – radiation). There should be a valid good manufacturing practice (GMP) contract with the irradiation site.

### Quality-assured sources for the API

It is recommended that the oxytocin API is procured from a manufacturer that has obtained WHO prequalification or that has obtained the certificate of suitability to monographs of the European Pharmacopoeia, confirming its suitable quality for use in a medicinal product. At the time of publication, there was only one oxytocin API prequalified by the WHO prequalification programme (39).

*Table 6. Manufacturer of oxytocin API prequalified by the WHO programme (39)*

WHO REFERENCE NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST PERIOD OR SHELF LIFE	DATE OF PREQUALIFICATION
WHO API-361	Hemmo Pharmaceuticals Pvt. Ltd	C-43, MIDC, Off Thane Belapur Road, TTC Industrial Area, Turbhe, Navi, Mumbai, Dist: Thane Maharashtra 400 613, India	Store in a refrigerator (2°C to 8°C), protect from moisture	36 months	25 September 2019

At the time of publication, there are five manufacturers of oxytocin API with a valid certificate of suitability to monographs of the European Pharmacopoeia.

*Table 7. Manufacturers of oxytocin APIs with certificates of suitability to the monographs of the European Pharmacopoeia (40)*

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE
Oxytocin (monograph number 780)	Aspen Oss, Netherlands	R1-CEP 2000-150-Rev 03	7 April 2016
Oxytocin (monograph number 780)	Hemmo Pharmaceuticals Pvt Ltd, India	R1-CEP 2008-029-Rev 00	16 October 2015
Oxytocin (monograph number 780)	Shanghai Soho-Yiming Pharmaceuticals Co, Ltd, China	R1-CEP 2011-003-Rev 00	25 August 2017
Oxytocin (monograph number 780)	Shenzhen JYMed Technology Co, Ltd, China	R0-CEP 2015-376-Rev 01	28 May 2020
Oxytocin (monograph number 780)	JSC Grindeks, Latvia	R1-CEP 2002-200-Rev 01	21 September 2018

Other manufacturers of oxytocin API should provide evidence for GMP compliance and API quality documentation in accordance with the WHO guideline (41).

## NOTES FOR REGULATORS

When assessing API quality documentation, regulators should pay attention to the controls on materials used in the manufacture of oxytocin API, especially the use of recovered solvents, which may introduce impurities.

The process to improve the quality of the recovered solvents should be described clearly, and demonstrated to be adequately controlled, such that impurity levels do not increase over time. The specifications of recovered solvents should include appropriate limits for assay, impurities and non-volatile matter (0.1 per cent). Any lessening of the quality limits of the recovered solvent needs to be justified. It should be demonstrated that any recovered solvents with impurity levels approaching the limits proposed afford an API of acceptable quality.

The use of recovered solvents in the final step of purification is not recommended; however, their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7 (42).

## API specification

The specifications of oxytocin API should be in line, as a minimum standard, with a pharmacopoeial monograph (such as The International Pharmacopoeia, European Pharmacopoeia, British Pharmacopoeia, United States Pharmacopoeia). Additional parameters to be considered are described in the 'Notes for regulators'.

## NOTES FOR REGULATORS

The pharmacopoeias differ in the parameters they set out. Careful consideration should thus ensure the following are appropriately controlled: specific optical rotation, bacterial endotoxins, water content, pH, acetic acid content and amino acid content.

Pharmacopoeial monographs of oxytocin API do not control specified impurities, so this should be added by the API/FPP manufacturer. As oxytocin is a synthetic peptide that is beyond the scope of the ICH Q3A guideline (impurities in new drug substances), the thresholds for reporting, identification and qualification of organic impurities should be based on the European Pharmacopoeia general monograph, 'Substances for pharmaceutical use':

- reporting threshold above 0.10 per cent
- identification threshold above 0.5 per cent
- qualification threshold above 1.0 per cent.

For residual solvents and elemental impurities that may arise during synthesis, the limits should comply with ICH Q3C (guideline for residual solvents) and Q3D (guideline for elemental impurities), respectively.

Microbial enumeration and specified tests for microorganisms should be considered for non-sterile APIs. If intended for use in the aseptic manufacture of oxytocin injection without a further appropriate sterilization procedure, the API must comply with the test for sterility.

## Container closure system

Oxytocin is hygroscopic and sensitive to light. It should be kept in an airtight container, protected from light, at a temperature of 2°C–8°C or, if sterile, in a sterile, airtight, tamper-evident container. A polyethylene container is common and suitable primary packaging for the API. For additional protection, the container is placed in a pouch (e.g. laminated foil bag or polyethylene-lined aluminium sachet).

When sterile API is used, aseptic sampling of sterile bulk API before dispensing for use in the manufacture of the FPP introduces an avoidable risk to sterility. For sterile APIs, sampling at the point of dispensing should be considered. Most companies producing sterile APIs will also provide side samples for the FPP site to perform release testing. Where side samples are provided by the supplier, the method and validation of sampling, sample size and its packaging must be initially assessed and agreed with the supplier (in the technical/supply agreement) and thereafter re-evaluated periodically. This supporting information should be maintained at the site but need not be submitted for assessment.

## NOTES FOR REGULATORS

Data submitted in the dossier should demonstrate the suitability of the proposed container closure system for use with the oxytocin.

For sterile oxytocin API, the applicant should discuss the sealing design and provide one-time data to demonstrate the integrity of the container-closure system by either a microbial or dye ingress test.

## Method of transport of API to manufacturer

Records should show evidence of cold storage (2°C–8°C) throughout transport. The container and the environmental conditions under which the API is transported from the API manufacturer to the FPP manufacturer, as well as the delivery time, are critical factors that could affect the quality of the API. Excessive heat and exposure to humidity or light, particularly if not suitably packaged, could initiate degradation.

Additional requirements and information are provided in existing guidelines, such as from WHO (43) and the United States Pharmacopeial Convention (44).

Detailed records of all the stages of transport, from the date the product leaves the API manufacturer to when it arrives at the FPP facility, should be provided so that the FPP manufacturer can be assured that the product has not been subject to adverse temperature or humidity for a potentially harmful length of time. Manufacturers of the FPP should reach agreement with the API manufacturer and/or distributor on the most suitable transport to protect the API from exposure to high temperatures. Data loggers or suitable temperature-time indicators can be used to alert the FPP manufacturer of any excursion during transportation.

## 2.3.2. Formulation and selection of excipients

### Qualitative and quantitative composition

Oxytocin injection is a sterile solution of oxytocin or a sterile dilution of oxytocin concentrated solution in water for injection. Most formulations contain 10 IU/mL oxytocin. Formulations of 5 IU/mL are marketed in some countries, but it is a less appropriate formulation with respect to cost and rational medicine use. Accordingly, the WHO prequalification team accepts applications for products containing 10 IU only.

List of possible excipients (based on the formulation of an innovator product, Syntocinon):

- chlorobutanol 0.5 per cent volume by volume (v/v)
- acetic acid
- ethanol
- sodium acetate
- water for injection.

Other qualitative compositions can be found on the approved products list maintained by the WHO prequalification team (39).

## NOTES FOR REGULATORS

Evidence should be submitted that demonstrates the selected mode of transportation does not compromise sterility. This is typically by testing container integrity, of filled and sealed containers that have been subjected to the actual or simulated transportation conditions. Samples should also be tested for physico-chemical tests. A copy of the standard operating procedure used for receiving the sterile API at the FPP site should be submitted with the application.

Table 8. List of possible excipients

PRODUCT	EXCIPIENTS						
	Chlorobutanol hemihydrate	Acetic acid	Sodium acetate	Ethanol	Sodium chloride	Sodium hydroxide	Water for injection
	Preservative	pH adjustment	Buffering agent	Co-solvent	Tonicity agent	pH adjustment	Vehicle
RH079 (JSC Grindeks, Latvia)	●	●	●	●	●	●	●
RH050 (Pt Sanbe Farma)	●	●	●	●	●	●	●
RH083 (Steril-Gene Life Sciences (P) Ltd, India)	●	●	●	●	●	●	●

**Key:**

Green dot = possibly included Red dot = unlikely to be included

## NOTES FOR REGULATORS

The equivalence of the generic oxytocin product with the comparator product should be demonstrated, and the applicant should provide comparative results of physico-chemical properties (e.g. pH, density, surface tension, osmolarity) for both the generic and comparator products. Appropriate comparator products for oxytocin injection are Syntocinon (oxytocin 10 IU/mL injection, Novartis or Sigma Tau Espana), Pitocin (oxytocin 10 IU/mL injection, PAR Sterile Products), oxytocin 10 IU/mL injection (West-Ward Pharmaceuticals), oxytocin 10 IU/mL injection (Fresenius Kabi) (39).

Demonstration of the compatibility of the oxytocin API and excipient is not required for excipients that are present in the comparator products (the summary of product characteristics or product leaflet of

the comparator product should be provided as evidence).

Where chlorobutanol is included in the formulation as an antimicrobial preservative, the amount used should not exceed that used in the comparator products. The amount of preservative should be at the minimum quantity needed to act effectively, and this should be supported by studies.

Excipients not contained in the comparator product should demonstrate compatibility with the API through chromatographic results (assay, purity). The choice of excipients, their concentration and their characteristics can influence the oxytocin FPP performance and therefore should be discussed relative to their respective functions.

## Specific recommendations for the excipients

The excipients should be controlled according to the requirements of the officially recognized compendial standard (The International Pharmacopoeia, European Pharmacopoeia, British Pharmacopoeia, United States Pharmacopoeia), and include a test for bioload or bacterial endotoxins.

### NOTES FOR REGULATORS

Specifications should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen or silicon for stoppers).

It is expected that the specification for excipients (as for non-sterile oxytocin API) includes a test for bioload or bacterial endotoxins. A limit for total viable count of not more than 10 colony-forming units (cfu) per gram is recommended.

When ethanol is used in the formulation, a test for benzene should be included in the specifications of ethanol.

## Acetic acid

Acetic acid is mainly used for pH adjustment. Some formulations may also include sodium hydroxide for this purpose. The pH adjustment is crucial for oxytocin stability because it was shown by Nachtmann and others that oxytocin is most stable between pH 3 and pH 5 (24). Have and others also reported that the degradation of oxytocin was pH- and temperature-dependent and followed (pseudo) first order kinetics (32). Degradation was fastest at pH 9, followed by

pH 7, pH 2 and pH 4.5. Oxytocin degradation in formulations between pH 2 and pH 9 follows Arrhenius kinetics, with the pH 4.5 formulation being most stable. This information is important for formulation development of oxytocin injection.

## Chlorobutanol

Chlorobutanol may not be present in some formulations because oxytocin injection 10 IU/mL is intended for single-dose use, which generally does not require an antimicrobial preservative. However, some manufacturers may add a preservative to mimic the formulation of a comparator product or as an adjunct in the aseptic processing of the product where there may be product exposure during transfer, filling or packing operations. As previously mentioned in this document, if chlorobutanol is included in the formulation as antimicrobial preservative the amount used should not exceed the level in the comparator product.

Where chlorobutanol is included in the formulation as an antimicrobial preservative, the assay of chlorobutanol (preservative content) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of chlorobutanol is below 90 per cent, its effectiveness should be established by appropriate studies (e.g. United States Pharmacopoeia or European Pharmacopoeia general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of chlorobutanol corresponding to the lower proposed acceptance criterion.

A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to its content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.



## NOTES FOR REGULATORS

Some manufacturers may claim that chlorobutanol acts as a chemical stabilizer, reducing degradation and allowing the product to be stored at 25°C. This claim is unfounded.

Chlorobutanol is known to hydrolyse at high temperatures to form acidic degradation products (45). As such, the pH reduction can be observed in oxytocin products containing chlorobutanol when stored at high temperature, which can in turn increase the rate of degradation of oxytocin. The oxytocin formulation that contains chlorobutanol should therefore include a buffering agent (e.g. sodium acetate) to maintain a higher pH to mitigate against the degradation of oxytocin catalysed in acidic conditions, and should be kept refrigerated (27). During the dossier review, be sure that chlorobutanol stability is properly addressed in the formulation development report and that the submitted stability data, including pH and degradation results, are supportive.

## 2.4. REQUIREMENTS FOR FINISHED PRODUCT MANUFACTURING

### 2.4.1. Manufacturing process

Oxytocin injection is a straightforward medicine to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of oxytocin injection is a standard process – conducted under

appropriate aseptic conditions – that includes the steps of preparation with pH adjustment, pre-filtration and sterile filtration, and filling and sealing of the ampoules/vials.

The exclusion of high temperature at all stages of the manufacturing process and during storage of the product is important to ensure that the product will be stable throughout its shelf life.

### Environmental conditions and monitoring

Environmental conditions and process temperature control are necessary. Since oxytocin API is hygroscopic, relative humidity control should be considered before the API is introduced in the solution. Maintain the temperature of dispensed oxytocin at 2°C–8°C. The API, after being dispensed, should be used as soon as possible to avoid exposure to light and oxygen.

The selection of the temperature conditions may depend on the length of each stage of production, the time between stages and how bulk solution is packed and stored. Suggested conditions for production are temperatures not more than 25°C ± 2°C.

### Compounding

Oxytocin API and chlorobutanol quantities should be calculated based on the actual assay and water content of the raw material batches used.

Nitrogen purging should be carried out throughout the manufacturing process to minimize the contact with atmospheric and dissolved oxygen. In case bulk solution storage is required, it is recommended to store the solution under a nitrogen blanket. The temperature of the bulk solution should be maintained preferably below 10°C ± 5°C. Validation data, including holding time, should support the storage duration and conditions defined by the manufacturer.

## Product sterilization/sterile filtration

Since oxytocin is susceptible to degradation by heat, terminal steam sterilization cannot be used. Oxytocin injection should be manufactured by aseptic technique for the whole process or sterile filtration of the bulk solution followed by aseptic filling.

The temperature of the bulk solution should be maintained preferably below  $10^{\circ}\text{C} \pm 5^{\circ}\text{C}$  until the end of filtration. Validation data, including holding time, should support the storage duration and conditions defined by the manufacturer.

The following in-process tests should either be present or their absence suitably justified.

- The bioburden should be determined immediately prior to final sterilizing filtration (total viable count of not more than 10 colony-forming units (cfu)/100 mL). Such low bioburden may be assured by limit testing in the case of a single filtration step or serial filtration with the monitoring of the bioburden earlier in the process.
- The integrity of filters should be confirmed before and after filtration and results should be recorded in the batch manufacturing records.
- The bacterial endotoxin level of the bulk solution before filtration should be controlled and periodically monitored.
- The sterile solution should be sampled and tested for visible particles and for the solubility of the API.
- Ampoules/vials sampled during filling and sealing should be tested for the absence of contaminating particulate/foreign matters.
- Leak testing of the filled and sealed containers should be conducted using a validated method.

## Process holding time

Avoiding long-term exposure of oxytocin to high temperatures, the time taken to transfer the API from the approved raw material store to the dispensing area and the time to dispense the API should be controlled and validated. The same controls should be considered for the storage time and the addition of the API to the manufacturing tank. Additional recommendations:

- The API must be maintained at  $2^{\circ}\text{C}$ – $8^{\circ}\text{C}$  until API is added to the manufacturing tank.
- The total holding time from transferring the API from the raw material storage area to the manufacturing tank should preferably be no longer than one work shift (eight hours).

## NOTES FOR REGULATORS

For aseptically processed FPPs, sterile filtration and filling into final containers should preferably be continuous. Any holding time prior to sterile filtration should be justified with supportive stability data (at a minimum, for appearance, pH, bioburden, related substances and assay).

## Filling

The filling process is a standard procedure that should comply with the GMP standards for filling sterile pharmaceutical product.

No particular concerns are related to the filling step. However, aiming to improve the stability of oxytocin, it is desirable to have nitrogen purging carried out throughout the filling process to minimize the contact with atmospheric and dissolved oxygen. If bulk solution storage is required it is also recommended to store the solution under a nitrogen blanket.

The fill volume should be monitored during filling.

### Process validation

No specific requirements for the validation of the oxytocin manufacturing process are required in addition to the general validation requirements of aseptic processing.

### Overages

No overage of the API should be used.

If sterilization of the solutions containing excipients is accomplished via filtration, loss of excipients present in the formulation in relatively small quantities (e.g. sodium chloride used in the formulation to set the tonicity) should be investigated.

## 2.4.2. Finished product specifications

The product should meet pharmacopoeial specifications, such as those of The International Pharmacopoeia, United States Pharmacopoeia and British Pharmacopoeia, as a minimum standard.

The minimum parameters to be included in the specification include appearance, identification, pH, assay, related substances, bacterial endotoxins, sterility, extractable volume and particulate matter. Additional recommendations are provided in 'Notes for regulators'.

## NOTES FOR REGULATORS

Testing parameters and acceptance criteria of the three pharmacopoeias are similar, but pH, related substances and bacterial endotoxin limits do differ. Regardless of the compendial standards used, additional in-house tests for other critical parameters should be included as appropriate. FPP specification should adhere to the guidelines in ICH Q6A (46).

As pharmacopoeial monographs of oxytocin injection do not control specified impurities, these should be added by the FPP manufacturer. Impurities above the identification threshold given in the European Pharmacopoeia general monograph, 'Substances for pharmaceutical use' (0.5 per cent) should be identified, and the limits above the qualification threshold (1.0 per cent) should be qualified. Data and details of the potential and actual impurities/degradation products of the FPP should be presented and discussed.

A limit of not more than 0.5 per cent for unspecified impurities should be included in the oxytocin FPP specifications.

Where an antimicrobial preservative (e.g. chlorobutanol) is included in the formulation, the assay of preservative should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of the preservative is below 90 per cent, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criterion.

The absence or inclusion of certain tests, the evolution of tests, analytical procedures, acceptance criteria or any other differences from international compendial methods/standards should be appropriately justified and discussed.

## 2.5. PACKAGING AND PRESENTATION

Oxytocin injection is generally packed in glass ampoules. However, some manufacturers provide the product in a glass vial, plastic vial or disposable syringe. Stability can be expected to vary significantly between different packaging materials; glass ampoules are considered most protective.

The container-closure system (ampoule/vial/disposable syringe) must be sufficient to preserve sterility during the shelf life of the product.

Some manufacturers may consider the use of a time-temperature indicator (TTI) on the packaging as a mechanism to know when the ampoule's heat exposure is likely to have degraded the oxytocin. TTIs mimic the degradation of the pharmaceutical product against time and temperature, with a safety margin, and are calibrated against the stability characteristics of a product. For example, one oxytocin product was designed to indicate a discard point at the equivalent of 17.2 days at 40°C, 72.5 days at 30°C and 154 days at 25°C.

### 2.5.1. Glass ampoule/vial

A neutral Type I glass ampoule or vial should be used.

- The glass ampoule/vial must meet compendial requirements such as USP<660> and USP<1660>.
- The rubber stopper (for vials) must meet compendial requirements such as USP<381> and USP<87>/USP<88>. Extractables/leachables data for the rubber stopper should also be provided.

**Note:** if applicable, the silicon oil used for the siliconization of rubber stoppers should be of pharmacopoeial grade.

Container integrity regarding microbial

contamination should be demonstrated by microbial or dye ingress or other methods:

- For vials, one-time test reported as part of product development;
- Routine leak testing performed as part of the product manufacture.

### 2.5.2. Plastic containers

- The packaging system must meet compendial requirements such as:
- USP <1663> (assessment of extractables associated with pharmaceutical packaging/delivery systems);
- USP <1664> (assessment of drug product leachables associated with pharmaceutical packaging delivery systems);
- USP <661.1> (plastic packaging systems and their materials of construction); and
- USP <661.2> (plastic packaging systems for pharmaceutical use).
- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
- One-time test reported as part of product development;
- Routine leak testing performed as part of the product manufacture.

### 2.5.3. Time-temperature indicators

If time-temperature indicators (TTIs) are used by the manufacturer, the regulator should ensure that:

- TTIs were incorporated in the packaging (for example, affixing them to blister-pack flats);
- TTIs are affixed at the point of manufacture to ensure that time and heat exposure are accounted for during warehousing and transportation up to the point of use; and
- Data related to the temperature sensitivity of the product are available and have been used to support the selection of the TTI. TTIs calibrated to approximate the temperature sensitivity of oxytocin more closely should be used.

Regulatory guidance developed for vaccine vial monitors may guide the evaluation of products using TTIs, including the performance, quality and safety (PQS) vaccine vial monitors performance specification (WHO/PQS/E06/IN05.2) and the PQS vaccine vial monitors independent type-testing protocol (WHO/PQS/E06/IN05.VP.2) – both available at [https://www.who.int/immunization\\_standards/vaccine\\_quality/vvm\\_documents](https://www.who.int/immunization_standards/vaccine_quality/vvm_documents).

### Notes for regulators

Accelerated and long-term stability data are expected for vials stored in an inverted orientation; this should further support the absence of leachables as well as sorption.

For the rubber stopper, where used, a declaration from the supplier that the material is free of 2 mercaptobenzothiazoles and nitrosamines should be provided.

Owing to a potential for water loss, oxytocin products proposed for packaging in semipermeable containers (commonly, plastic ampoules) should undergo accelerated stability studies in conditions of low relative humidity (40 per cent or lower). Alternatively, as described in stability guidelines from WHO (47) and ICH, the applicant can perform the stability studies under higher relative humidity and calculate the water loss at the low relative humidity.

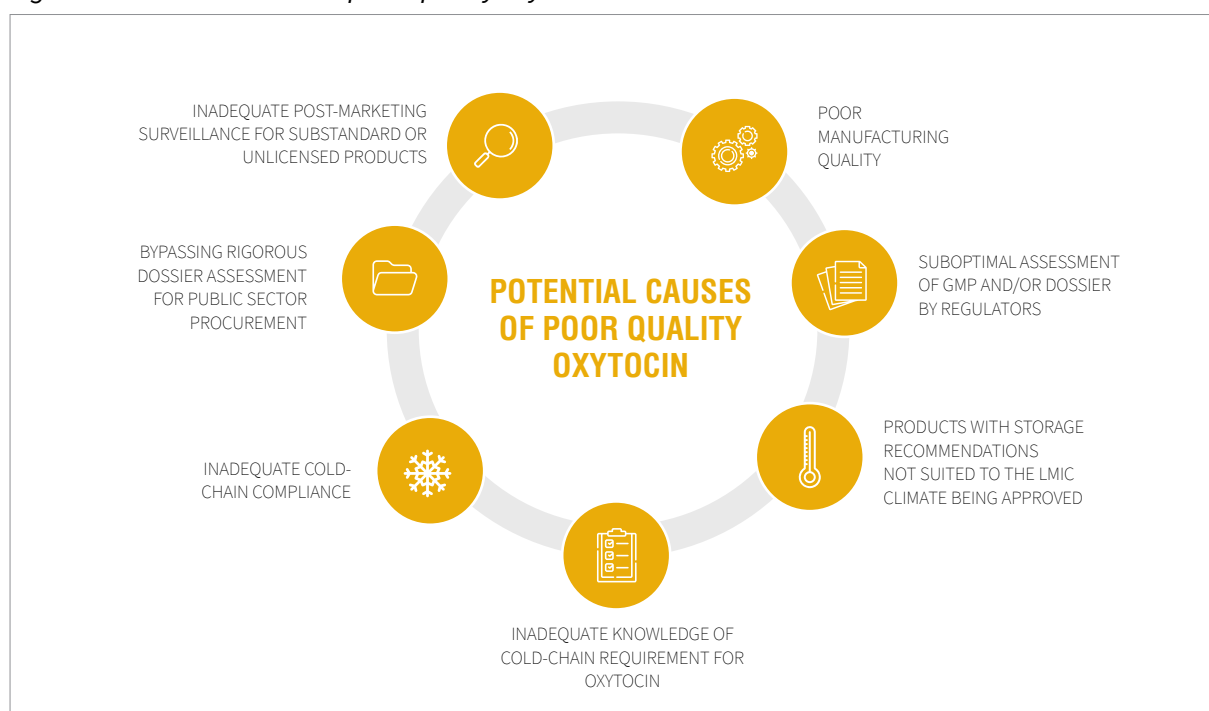


### 3. RECOMMENDATIONS

The problem of poor oxytocin quality has been demonstrated by research findings across low- and middle-income countries (LMICs). The causes are multifactorial and country context-specific, and may include (Figure 5):

- Poor manufacturing quality;
- Suboptimal assessment of good manufacturing practice (GMP) and/or of the dossier of oxytocin products by regulators;
- Products with storage recommendations not suited to the LMIC climate being approved;
- Inadequate knowledge of cold-chain requirements for oxytocin;
- Inadequate cold-chain compliance;
- Bypassing of rigorous dossier assessment for public sector procurement; and
- Inadequate post-marketing surveillance to identify and remove substandard or unlicensed products.

Figure 5. Potential causes of poor-quality oxytocin



Robust regulatory oversight in the manufacturing, marketing authorization, cold chain storage and procurement of oxytocin is crucial to ensure the safety and quality of this life-saving commodity. National medicines regulatory authorities have the responsibility and authority to evaluate and identify the extent of oxytocin quality issues in their countries, to determine the root causes and to take appropriate corrective and preventative actions

to address each causative factor. Tables 9 to 11 highlight steps that could be considered by the authorities, both during dossier assessment and more generally to control all oxytocin products in their markets. Note that national medicines regulatory authorities should ensure that regulatory actions are taken in ways that do not cause interruptions to the supply of this critical maternal health product.

Table 9. Key dossier assessment considerations for regulators

<b>1</b>	Accept new dossier applications only for products labelled for storage according to the WHO/ UNICEF/UNFPA joint statement (7): ‘Store in a refrigerator (2°C to 8°C), do not freeze, protect from light’.
<b>2</b>	Where oxytocin products are proposed for registration using Reference Regulatory Authority recognition procedures, ensure the submitted stability data adequately support storage at 2°C–8°C. Products authorized by the reference regulatory authorities that are labelled for storage up to 25°C (77°F) cannot be considered suitable for use in LMICs classified as Climatic Zones III or IV.
<b>3</b>	Formulations containing antimicrobial preservatives should be given careful consideration, ensuring acceptable manufacturing process and environment are proposed and that the inclusion of the preservative does not compensate for a lower manufacturing standard. The oxytocin formulation that contains chlorobutanol should include a buffering agent (e.g. sodium acetate) and be kept refrigerated to mitigate against oxytocin degradation.
<b>4</b>	Pharmacopeial specifications for oxytocin active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) represent the minimum standard. The adequate control of critical parameters should be considered thoroughly.

Table 10. Other key steps to be considered by regulators

	RECOMMENDATION	IMPLEMENTATION CONSIDERATION
<b>GAP ASSESSMENT AND DISSEMINATION</b>		
<b>1</b>	Identify priority areas where this guidance would be beneficial	Disseminate this guidance as appropriate
<b>2</b>	Evaluate the skills and knowledge of relevant regulatory officials in the assessment and regulation of oxytocin products, in line with this document, and identify any subsequent training needs	Conduct training as appropriate across regulatory mandates: to address oxytocin product quality concerns, recommended dossier assessment requirements, and post-marketing surveillance requirements
<b>POST-MARKETING SURVEILLANCE AND PHARMACOVIGILANCE</b>		
<b>3</b>	Evaluate if products are available on the market without valid registration or with temporary authorization	Strengthen regulatory resilience in the removal of unauthorized oxytocin products from the market



4	Evaluate the quality of all currently registered or temporarily authorized oxytocin products by carrying out targeted post-marketing surveillance activities, including sampling and testing	Regulatory actions such as product recalls or safety alerts where post-marketing surveillance identifies out-of-specification products Establishment of follow-up post-marketing surveillance activities to assess the impact of corrective actions taken
<b>STORAGE RECOMMENDATIONS</b>		
5	Evaluate the labelled storage recommendations of all currently registered or temporarily authorized oxytocin products	Engagement with marketing authorization holders about any product labelling concerns identified
6	Regardless of labelled storage condition, recommend storage of oxytocin products at 2°C–8°C	Refer to guidance detailed in the WHO/UNICEF/ UNFPA joint statement on the appropriate storage and management of oxytocin (7)
<b>REGULATORY OVERSIGHT ON OXYTOCIN COLD CHAIN</b>		
7	Evaluate the cold chain compliance of oxytocin transport and storage in public and private supply chains	Disseminate information, including training activities, to all relevant stakeholders to ensure awareness of the cold chain storage requirement of oxytocin products. Stakeholders may include, procurement agencies, supply chain managers, maternal, newborn and child health (MNCH) programme leaders, Expanded Programme on Immunization (EPI) managers, port of entry officers and relevant customs warehouses staff  Encourage coordination between EPI managers, MNCH programme leaders, and supply chain managers to consider whether oxytocin would benefit from being integrated into the national EPI cold chain, and implement if appropriate
<b>PUBLIC PROCUREMENT</b>		
8	Consider whether appropriate mechanisms are in place to ensure the quality of oxytocin products procured by government procurement agencies without formal national registration	Restrict the issuance of temporary authorizations by procurement agencies to oxytocin products either prequalified by WHO, recommended by the WHO expert review panel, or registered by a stringent regulatory authority*, and labelled for storage at 2°C–8°C (35°F–46°F)

*\*The reference regulatory authority could be similar to the previously named stringent regulatory authority: a regulatory authority that is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the United States Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally binding, mutual-recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (48).*

*Table 11. Examples of implementation steps for this guidance*

<b>1</b>	Provide training on this document to all regulatory officers with responsibility for the assessment of oxytocin dossiers or oxytocin post-marketing surveillance
<b>2</b>	Audit oxytocin products registered in the local market. Identify products available in both public and private sectors, review regulatory status, review labelling and dossiers, carry out quality-control testing
<b>3</b>	Audit the supply chain for oxytocin. Identify current compliance with cold chain storage, and ensure awareness of the cold chain requirement among health-care workers, supply chain managers and maternal health programme staff
<b>4</b>	Set up meetings with stakeholders to discuss and agree on corrective actions identified in the above audits
<b>5</b>	Issue a safety update to say that all oxytocin products must be stored in a refrigerator irrespective of labelling, and advise that products with inappropriate labels for your country will be carefully phased out
<b>6</b>	Contact the marketing authorization holders of oxytocin products with inappropriate labelling to request they change the labelling of their products within a set timeframe, and/or provide supporting stability data
<b>7</b>	Develop and publish new requirements for oxytocin product registration

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## REGULATORY GUIDANCE FOR ASSESSMENT AND MANAGEMENT OF APPLICATIONS FOR MARKETING AUTHORIZATION OF OXYTOCIN

Injectable oxytocin, given intravenously or intramuscularly, is recommended by the World Health Organization as the first-line medicine for the prevention and treatment of postpartum haemorrhage. It is additionally used for the induction and augmentation of labour, is included in the WHO Model List of Essential Medicines and is one of 13 priority life-saving medicines listed by the UN Commission on Life-Saving Commodities for Women and Children. It is an inexpensive medicine that is widely manufactured and distributed.

Studies have identified high rates of substandard oxytocin in many LMICs, both in products that have achieved formal regulatory approval and those that have not. The primary causes for substandard oxytocin quality are considered to be poor-quality manufacturing and/or product degradation in the supply chain. Each of these factors points to critical responses needed from national medicines regulatory authorities, both on the quality of oxytocin manufacturer and dossier assessments, and on stronger regulatory oversight of oxytocin in markets.

Pharmaceutical regulators are at the forefront of ensuring that only safe and effective medicines are authorized and available in the market. This guidance document has been prepared to specifically assist national medicines regulatory authorities to understand the nature and extent of oxytocin quality issues and to provide key technical information and quality requirements for oxytocin products in dossier assessments. Furthermore, this guidance also provides recommendations on other regulatory actions needed to ensure that only quality-assured oxytocin products are authorized and made available to women.

While the primary target audience is pharmaceutical regulators in national medicines regulatory authorities, the information may also assist manufacturers in the development of quality oxytocin. It may similarly assist procurers involved in identifying or prequalifying oxytocin products for procurement.

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