PQM Promoting the Quality of Medicines

Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review

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Acronyms

API	active pharmaceutical ingredient
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPP	finished pharmaceutical product
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
LMIC	low- and middle-income country
PPH	postpartum hemorrhage
PQM	Promoting the Quality of Medicines (program)
PQT	Prequalification Team
RH	relative humidity
TTI	time–temperature indicator
UNFPA	United Nations Population Fund
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopoeia
WHO	World Health Organization

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1. Objective

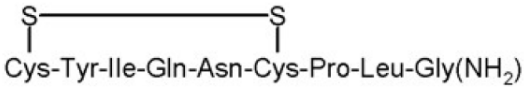
Oxytocin is used in the management of pregnancy-induced postpartum hemorrhage (PPH). PPH is excessive bleeding after delivery, within the 24-hour period after birth, leading to anemia and shock and, in some cases, death. Although oxytocin, administered as an intravenous injection, is effective in preventing maternal deaths, significant challenges limit access of quality medicine, particularly to women in developing countries. The present summary is a critical analysis of the published literature, aimed to delineate the effect of various factors that compromise the quality of oxytocin injection available in low- and middle-income countries (LMICs). The review starts with a basic introduction to oxytocin as an active pharmaceutical ingredient (API) and as an injection formulation, followed by a compilation of research studies to establish the solution-state stability of oxytocin. We present a critical review highlighting results as well as limitations of various studies conducted to determine the quality of oxytocin available in LMIC markets. It is realized that improvement in quality of accessible healthcare products, such as oxytocin, is a critical component in efforts to reduce maternal mortality.

2. Introduction

2.1. Oxytocin Active Pharmaceutical Ingredient (API)

Oxytocin is a nonapeptidic hormone that is released from the posterior lobe of the pituitary gland of the hypothalamus. Therapeutically, it is used to induce or stimulate labor and to prevent post-partum hemorrhage. PPH is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one-quarter of all maternal deaths globally. Oxytocin is recommended by the World Health Organization (WHO) as the first drug of choice for these situations (WHO 2012). It is included in the Essential Medicines List in the life-saving commodities list developed by the United Nations Commission on Life-Saving Commodities for Women and Children's Health and the United Nations Population Fund (UNFPA).

Oxytocin molecule consists of a six-amino acid ring (Cys1, Tyr2, Ile3, Gln4, Asn5, Cys6) and a tail of three amino acids (Pro7, Leu8, Gly9-NH2).



Asn5 and Tyr2 are the key moieties required for proper function at the active site of the uterine receptor, and Ile3, Gln4, Pro7 and Leu8 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.

2.2. Oxytocin Injection Formulation

Oxytocin for injection is available in 1 mL ampoules, 1 mL disposable syringes, and in 1 mL or 10 mL vials. Each milliliter contains oxytocin 10 units and chlorobutanol 0.5% v/v. Syntocinon (Novartis) also incorporates ethanol (0.61% v/v) into the formulation. Acetic acid may be added to adjust the pH during manufacture. WHO-approved product RH 053 (JSC Grindeks, Latvia) lists the following excipients: acetic acid (glacial), sodium acetate trihydrate, sodium chloride, sodium hydroxide, and water for injection.

USP cites the pH range as 3 to 5. The commercial product from Fujisawa also listed the pH range to be 3 to 5. The American Hospital Formulary Service cites a pH range of 2.5 to 4.5 (Trissel 2001). Injection formulations of oxytocin approved by WHO, the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada are summarized in Table 1.

Table 1. Injection Formulations of Oxytocin Approved by Different Regulatory Bodies

Regulatory Body	Reference Number	Applicant	Status	Dosage Available
WHO	RH053	JSC Grindeks, Latvia	Oxytocin-Grindeks	5 IU/mL; 10 IU/mL
WHO	RH050	PT Sanbe Farma	Oxytocin injection	10 IU/mL
FDA	200219	Hikma Farmaceutica	Oxytocin injection	10 IU/mL
	018243	West-ward Pharmaceuticals	Oxytocin injection	10 IU/mL; 100IU/10mL
	018248	Fresenius Kabi USA	Oxytocin injection	10 IU/mL; 100IU/10mL 300 IU/30 mL
	018261	Par Sterile Products	Pitocin	10 IU/mL; 100IU/10mL 500 IU/50 mL
EMA	–	Grindeks	Oxytocin Grindeks	10 IU/mL (injection) 8.3 µg/mL (concentrate) 16.7 µg/mL
	–	Ebb Medical	Oxytocin Ebb	8.3 µg/mL (concentrate)
	–	Pilum Pharma	Oxytocin Pilum	8.3 µg/mL (concentrate)
	–	Omnia Pharmaceutical	Syntocinon	8.3 µg/mL (concentrate)
	–	Novartis Pharma Schweiz AG	Syntocinon	5 IU/mL
Health Canada	141828	Bimeda-Mtc Animal Health Inc.	Oxytocin injection	20 IU/mL
	2139561	Fresenius Kabi Canada Ltd	Oxytocin injection	10 IU/mL
	497398	Hospira Healthcare Corporation	Oxytocin injection	10 IU/mL
	2209446	Medprodex Inc.	Oxytocin injection	10 IU/mL
	2288931	Rafter 8 Products Inc.	OXY-20 NW	20 IU/mL

3. Stability Concerns for Oxytocin Formulations

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. 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 percent of the labeled claim. This can be a critical constraint in LMICs, where consistent and reliable cold-storage capability is often lacking.

Drug degradation has safety and efficacy implications, and the degradation of the active ingredient can lead to the formation of toxic decomposition products. However, as a peptide, the degradation products of oxytocin are not toxic. Therefore, while degradation may not necessarily be a safety issue, specifically in the case of oxytocin (Hodgins and Lukulay, 2017), it can still lead to a reduced API level and hence compromised performance. The following discussion highlights the disparity in recommended storage conditions by different pharmacopoeias and by manufacturers around the world.

3.1 Storage Conditions and Monograph Specifications

Storage Conditions

While it is recommended to store oxytocin between 2°C and 8°C, there is no consensus on the appropriate storage conditions for the API and the dosage form (Table 2). Though there is a general requirement to store API at 2°C to 8°C, the requirement for protection from light and/or moisture is not consistent among pharmacopoeias. Surprisingly, British Pharmacopeia, International Pharmacopoeia, and U.S. Pharmacopeia are silent with respect to storage temperature for the finished dosage form. Current International Pharmacopoeia guidelines recommend storing oxytocin at 2°C to 8°C and protecting it from light exposure.

On the basis of a comprehensive study conducted in 1993, WHO recommends storage under refrigeration (2°C to 8°C) whenever possible. It is acceptable to keep oxytocin injections unrefrigerated for short periods of time: no more than 1 month at 30°C, or 1 week at 40°C (Pribluda et al. 2012; Hogerzeil et al. 1993).

Table 2. Comparison of Storage, Labeling, and pH Specifications for Oxytocin and Oxytocin Injections, as Recommended by Different Pharmacopoeias

	Storage Temperatures		Labeling		pH	
	API	FPP	API	FPP	API	FPP
USP 40	Preserve in a refrigerator*	(*Note: monograph is silent on storage temperatures*)†	*Complies with USP <7> Labeling requirements*	Indicate oxytocic activity in USP Oxytocin Units per mL; 90.0%–110.0%	*(Note: monograph is silent on pH)*	3.0 to 5.0
European P, 9th Edn‡	2°C–8°C, protected from light	2°C–8°C, protected from light	State the oxytocin peptide content†	State the peptide content in mg per mL†;95.0–105.0%	3.0 to 6.0	3.0 to 5.0†
Int P 2016 6th Edition	2°C–8°C protected from light	2°C–8°C unless otherwise indicated on the label	"Where applicable:" it is free from bacterial endotoxins; it is sterile	Content in IU per mL and oxytocin peptide content in mg per mL; 90.0%–110.0%	pH of 20 mg/mL in carbon-dioxide-free water is 3.0 to 6.0	3.0 to 5.0
BP 2018	2°C–8°C	(*Note: monograph is silent on storage temperatures*)	State the oxytocin peptide content	State number of IU (Units) per mL and equivalent µg of oxytocin per mL; 90.0%–110.0%	3.0 to 6.0	3.5 to 4.5
JP 17th Edn, 2016	2°C–8°C	Cold place and avoid freezing. A cold place, shall be 1°C–15°C	Labeled oxytocin Units§	Contains 90.0%–110.0% of the labeled oxytocin Units§	0.10 g in 10 mL freshly boiled and cooled water is 4.0 to 6.0	2.5 to 4.5
Indian Pharmacopoeia 2014	Store protected from moisture (*Note: silent on temperature requirements*)	*(Note: monograph is silent on storage temperature for FPP).*	Label states (1) give units of oxytocic activity per mg (for solid) or per mL(for liquid); (2) name source animal species or synthetic source; (3) whether or not contents for use in manufacturer of parenteral preparations	The label states (1) the number of Units of oxytocin activity per mL; (2) either the animal species from which is obtained or synthetic source; 90.0%–110.0% of the stated number of Units of oxytocin activity	*(Note: monograph is silent on pH)*	3.0 to 5.0
Indian Pharmacopoeia 2018	Same as Indian Pharmacopoeia 2014	Same as Indian Pharmacopoeia 2014	Same as Indian Pharmacopoeia 2014	Same as Indian Pharmacopoeia 2014	Same as Indian Pharmacopoeia 2014	3.0 to 5.0

* U.S. Pharmacopoeia does not specify the temperature range for a refrigerator.

† Explicit temperature requirements were removed from the section, proposed in PF32(6) effective in USP31, manufacturers should label storage requirements for their product based on their storage studies.

‡ EP does not have oxytocin Injection monograph, it has oxytocin concentrated solution monograph. BP allows preparation of oxytocin injection from oxytocin and oxytocin concentrated solution.

§ The origin, numerical value, or physical properties of JP Drugs, being stipulated by the special labeling requirements in the monographs, have to be shown on the immediate container or wrapping of them, JP XVII.

The storage conditions for oxytocin injections suggested by manufacturers on the label are also quite variable. Novartis (earlier Sandoz) recommends storage at "room temperature" (15° to 25°C) and protected from freezing. Do not use the solution if it is discolored or contains a precipitate" (Trissel 2001). Table 3 summarizes the storage conditions listed on the label and the corresponding shelf-life for products manufactured in 6 countries by 15 manufacturers. Samples were collected as part of a study conducted by WHO(WHO 2015).

Table 3. Recommended Storage and Shelf Life of Products Manufactured in Different Countries (WHO 2015)

S. No.	Name of Manufacturer	Country of Manufacture	Country of Collection	Recommended Storage	Shelf Life
1	Zhejiang Tianfeng Pharmaceutical	China	Uganda, Burkina Faso	Store in cool and dark place	3 years
2	Zhejiang Ruixin Pharmaceuticals 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	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 Pharmaceuticals	India	Nepal	Do not freeze	2 years
8	Umedica Laboratories Pvt Ltd,	India	Nepal, Kenya	Not exceeding 30°C	3 years
9	Tablets India Ltd,	India	Vietnam	Not exceeding 30°C, do not freeze	2 years
10	Kwality Pharmaceutical (P) Ltd	India	Nigeria	2°C to 8°C, protect from light and heat	3 years
11	Akums Drugs and Pharmaceuticals Ltd	India	Nepal	Store in a cold and dark place, do not freeze	2 years
12	Rotexmedica GmbH Arzneimittelwork	Germany	Burkina Faso, Tanzania, Vietnam	2°C to 8°C, do not freeze	3 years
13	Biologici Italia Laboratories	Italy	Zimbabwe	Below 25°C, protect from light	2 years
14	Bryntsalov – A ZAO	Russia	Tajikistan	8°C to 20°C, protect from light	3 years
15	Gedeon Richter Plc	Hungary	Tajikistan	2°C to 15°C, protect from light	3 years

As is evident from the table above, there are discrepancies in the recommended storage conditions as well as in the shelf life of oxytocin injections from different manufacturers collected in the same country.

Monograph Specifications

As mentioned above, there is no general consensus among various pharmacopoeias in terms of the recommended storage conditions for API and dosage form. A detailed comparison of these specifications of oxytocin API and finished dosage form in seven pharmacopoeias is presented in Table 2 and Appendix Tables A1–A6. As these tables show, there are inconsistencies in terms of the source of oxytocin, measurement units, storage specifications, labeling requirements, and numerous other general compendial requirements. In general, the source of oxytocin API should be synthetic, although natural (animal) oxytocin is also allowed by IP and USP. Oxytocin content as API may be presented as a percentage, Oxytocin Units or USP Oxytocin Units. Hence the acceptance criteria for assay also vary depending upon the measurement units. For injections, while most of the pharmacopoeias recommend content of oxytocin within 90.0% to 110.0%, European Pharmacopoeia has more stringent acceptance criteria at 95.0% to NMT 105.0%. The contents of active API in injection are recommended to be expressed in different units such as IU/mL, ug/mL, mg/mL, oxytocin activity per mL, oxytocin units, and USP oxytocin Units per mL. European Pharmacopoeia does not have a monograph for the oxytocin injection. Instead, it has oxytocin concentrated solution monograph. BP allows preparation of oxytocin injection from oxytocin and oxytocin concentrated solution. Such inconsistencies have complemented the uncertainty associated with the recommended storage and labeling requirement for oxytocin injections.

3.2 Pharmacopeial and Stability-Indicating Assay

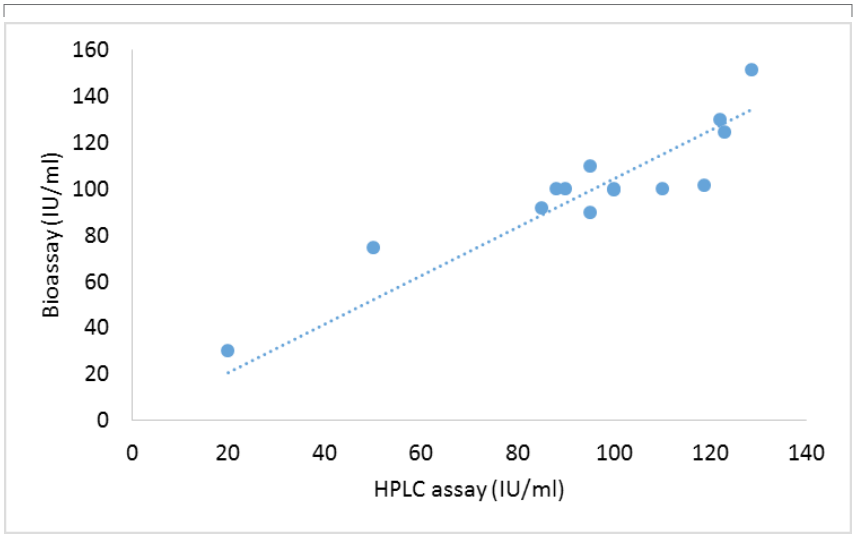
In accordance with the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines, “a stability-indicating method is defined as a validated quantitative analytical method that can detect the change with time in the chemical, physical, or microbiological properties of the drug substance and drug product and that are specific so that the contents of active ingredients, degradation products, and other components of interest can be accurately measured without interference.” The ICH Q1A (R2) guideline for stability explicitly requires conduct of forced decomposition studies under a variety of conditions such as pH, light, oxidation, dry heat, and so on, and separation of drug from degradation products. The stability-indicating method is expected to allow analyses of individual degradation products. The method emphasizes the requirement of validation and the requirement of analysis of degradation products and other components, apart from the active ingredient (ICH 2003).

As was previously mentioned, the optimum pH range for oxytocin is 3 to 5. In strongly acidic solutions, the peptide linkage undergoes hydrolysis. Under neutral and weakly alkaline conditions, dimeric and polymeric compounds are formed, especially in the concentrated solutions, by conversion of the intramolecular disulfide bridges of two or more oxytocin monomers to intermolecular bridges (disulfide interchange) (Ressler and Popence 1973). Thus, a stability-indicating method for oxytocin should be able to distinguish oxytocin from its degradation products.

Historically, most pharmacopoeias assayed oxytocin using the chicken blood pressure method or rat uterus method. High-performance liquid chromatography (HPLC) is now the method of choice in all official compendia. The isocratic and gradient elution-based methods have been shown to be sufficiently specific to separate oxytocin from synthesis byproducts (e.g., stereoisomers of the active compound) or related peptides (e.g., 8-lysine vasopressin) (Krummen and Frei 1977; O’Hare and Nice 1979).

Krummen and Frei (1977) estimated the oxytocin content of injections and concentrates with isocratic elution using acetonitrile and phosphate buffer. The HPLC results correlated well with those obtained by bioassay in a rat uterus test for 38 different batches of oxytocin (Figure 1).

Figure 1. Correlation between the results of bioassay (rat uterus method) and HPLC assay of oxytocin



Note: plotted from data in Krummen and Frei, 1977).

The compendial method for oxytocin in the current *USP* and *European Pharmacopoeia (Ph. Eur.)* is the HPLC gradient elution method (L1 column; octadecyl silane chemically bonded to silica) using a phosphate buffer and acetonitrile as mobile phases. No information is published in the aforementioned compendia with respect to the stability-indicating status of these methods (Chaibva and Walker 2008). Furthermore, no reports suggest that the current compendial methods can distinguish oxytocin from the degradation products.

Chaibva and Walker (2008) reported an oxytocin specific stability indicating isocratic HPLC method, in the presence of degradation products and chlorobutanol (preservative). In another study, an optimized gradient reverse phase HPLC method was developed and validated for identification and separation of various degradation products of oxytocin (Hawe et al. 2009).

3.3. Stability Studies for Climate Zone IVa and b

Climatic conditions affect the availability of quality oxytocin injection in LMICs and the differences in climatic conditions in varying regions of the world need to be taken into consideration when planning stability studies that determine the shelf life of drugs. Based on world climatic data, stability conditions for different climatic zones have been proposed (Grimm 1986/1988). Zone I was defined as temperate; Zone II subtropical or Mediterranean; Zone III hot and dry; Zone IVa hot, humid, and tropical; and Zone IVb hot and higher humidity. Based on these zones, a unified approach was proposed to perform stability studies at 25°C/60% relative humidity (RH) for long-term testing in the United States, European Union, and Japan, all in climatic Zone II (ICH 2003). For products to be marketed in Zone IV countries, long-term stability studies must be conducted at 30°C, with RH either 65% (Zone IVa) or 75% (Zone IVb). For parenteral products, stability data need to be provided at 30°C, on at least one

package configuration. The exclusion of humidity in the recommended conditions for stability studies of parenteral is specific to drug products packaged in impermeable containers (Seever and Schantz-Shirley 2011). The classification of packaging as moisture impermeable should be evaluated based on moisture vapor transmission rate data. Though a glass vial with a rubber stopper is not automatically defined as impermeable by any regulatory authority, properly sealed glass ampoules are considered to be moisture impermeable (WHO 2009). Oxytocin injection, a parenteral product, should be subjected to stability studies at 30°C. This may raise serious concerns, as outlined in the next sections.

4. Controlled Laboratories Stability Studies

As mentioned above, the ICH Q1A (R2) guideline for stability explicitly requires conduct of forced decomposition studies under a variety of conditions (such as pH, light, oxidation, and dry heat) and separation of the drug from degradation products. The stability-indicating method is expected to allow analysis of individual degradation products. A summary of the reports documenting systemic study of oxytocin stability in solution is presented below.

Oxytocin concentrates (200 IU/mL; pH 3.5) stored at various temperatures for 48 months were evaluated regularly for biological activity on rat uteri. Concentrates kept in a refrigerator showed no loss of oxytocin activity. Samples kept at 21°C showed a slight loss of activity about (1.5% per year), whereas those at 30°C showed a marked loss of activity (about 10% per year). Similar results were obtained with dilute injections of oxytocin. The study concluded that oxytocin in solution has a shelf file of 3 years at 21°C but should not be exposed to higher temperatures (Nachtmann et al. 1981).

In a simulation study conducted by WHO in collaboration with IDA Foundation, two batches of three brands of oxytocin ampoules were stored at different temperatures and samples were assayed for oxytocin content over a period of 2 years (Hogerzeil et al. 1993). Based on the results (Figure 2), WHO and IDA suggested the following guidelines for the shelf life of oxytocin injections at higher temperatures:

- At 2°C- 8°C, shelf life of 3 years.
- Below 21°C, shelf life of 2 years.
- 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 transport maximum 1 week.

Figure 2. **Results from stability studies of oxytocin injections stored at different temperatures for 2 years**

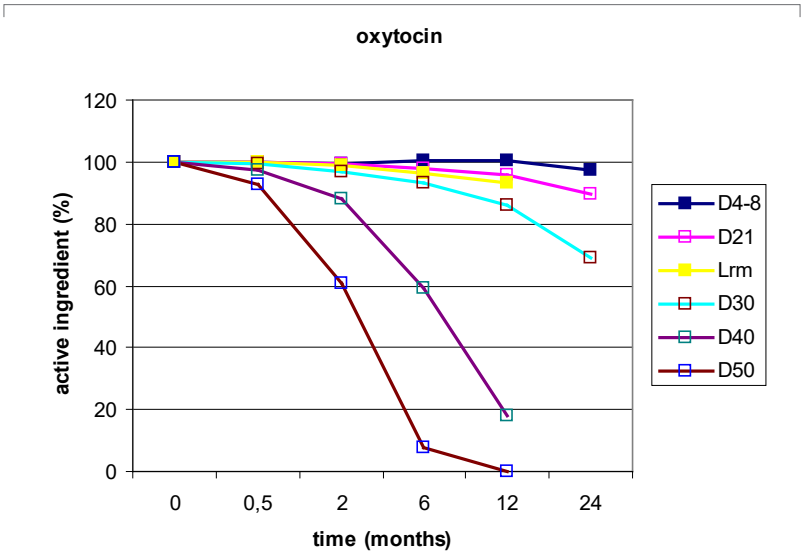


Figure legends correspond to the storage temperature and light (L)/dark (D) conditions. Lrm reflects storage at 21°C. Light had no destabilizing effect (contrary to information provided by the innovator) (Hogerzeil et al. 1993).

Hawe et al. reported degradation kinetics of oxytocin formulated at pH 2.0, 4.5, 7.0. and 9.0 and performed at 40°C, 55°C, 70°C, and 80°C. Degradation rate constants were determined from reversed phase-HPLC data, and degradation products were identified by electrospray ionization mass spectrometry. Degradation of oxytocin followed first order kinetics (Hawe et al. 2009) at all temperatures, and solutions were most stable at pH 4.5. This study was conducted at elevated temperatures from 40°C to 80°C. However, it is important to estimate degradation kinetics of oxytocin solutions at pharmaceutically relevant temperatures. Assuming the mechanism of degradation remains unchanged, we extrapolated the first order rate constant for oxytocin degradation to lower temperatures and estimated the $t_{90\%}$ (time for 10% drug decomposition) at pH 4.5 (the pH range of oxytocin formulation is 3 to 5, as per USP).

S. No.	Temperature (°C)	K ($days^{-1}$)	$t_{90\%}$ (days)
1	40	6.00E-4	17
2	35	2.77E-4	38
3	30	1.28E-4	82
4	25	0.57E-4	183

These calculations indicate loss of 10% activity, if oxytocin solution is stored at 30°C for ~3 months. Official specifications require that each mL of oxytocin injection possess activity of not less than 90 (the lower limit) of that stated in the label in USP oxytocin units. The above data suggest that when stored at ≥ 30°C, the shelf life of the formulation (2 to 3 years; refer to Table 3) is critically compromised.

5. Stability of Marketed Formulations

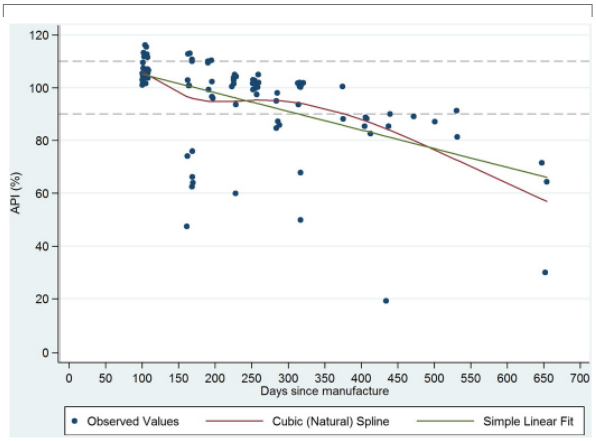
With the preceding discussion highlighting the scientific rationale, it is worthwhile to assess the stability of oxytocin injections in real-life scenarios. Several studies have raised the issue of poor-quality oxytocin in terms of drug content (and sterility) at the point of sale in LMICs, especially in Africa and Asia. In a survey by a WHO Prequalification Team (WHO PQT) working with 13 marketed products (9 injections and 2 tablets), the highest proportion of noncompliant samples was found for oxytocin injections (64%; WHO 2015). Possible causes for substandard oxytocin products include quality of manufacturing and inappropriate conditions throughout the supply chain (a system of organizations, people, activities, information, and resources involved in moving a product from the supplier to the end user in a manner that ensures the good quality of the product until it is consumed) (Torloni et al. 2016).

In 1993 and 1994, WHO supported a number of studies that demonstrated that oxytocin loses potency in field conditions, particularly in tropical climates (Hogerzeil et al. 1993; DeGroot et al. 1994). Several studies highlight the substandard quality of some of the essential medicines available, including oxytocin injections, mainly in Asia and Africa. A summary of the studies and the results of the quality of oxytocin injections are outlined below:

- A USAID/USP sponsored study was conducted to assess the quality of available oxytocin injections in samples collected in Indonesia. Major commercial and generic brands (total 110 ampoules) were assayed using the USP 33 method. The overall 11.8-percent failure rate in assay (out of specification) highlighted a serious problem with the quality of oxytocin injections at sampling sites. The study also suggested the importance of storage conditions as the failure rates for refrigerated and non-refrigerated samples were 11.9 percent and 15.8 percent, respectively. However, a strong correlation was not established due to the limited number of samples. The study concluded that (1) storage in a controlled environment is not a common practice and (2) lack of specific guidelines during transportation, supply, and distribution is one of the potential issues to be addressed (Pribluda et al. 2012).

- Stanton et al. (2014) conducted a study to assess the potency of oxytocin ampoules in pharmacies in two states in India. API content was determined in 193 ampoules using the HPLC method using USP 33. The percent of oxytocin ampoules outside of specification ranged from 33 percent to 40 percent in Karnataka and from 22 percent to 50 percent in Uttar Pradesh. The API content immediately after manufacture, at or along the supply chain, is unknown. Hence, it is difficult to assess the exact cause of the high failure rate. Data in Figure 3 suggest an approximate loss of API ranging from 3.6 percent to 6.4 percent over 90 days for oxytocin samples and is suggestive of drug degradation.

Figure 3. Oxytocin contents in injections plotted against time since manufacture



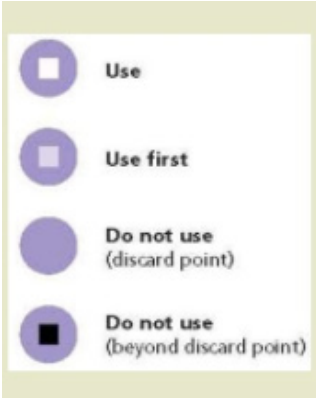
Source: Stanton et al. (2014)

- In another similar study conducted in Ghana, 46 samples of oxytocin ampoules were purchased from different sources in three districts. The Ghana Food and Drugs Board used the BP method to determine drug content. Only 11 (26%) samples were within official specifications, and 2 (4%) were expired. The median percentage of API content was 64 percent. The study highlighted a serious problem with the quality of injectable uterotonics at the peripheral level in Ghana (Stanton et al. 2012).

- A detailed study was conducted by Ghana FDA and PQM/USP to confirm whether oxytocin injections available in the Ghana market aligned with the specifications and standards listed by the manufacturer. A total of 185 oxytocin ampoules were collected from 10 sites. During sampling, it was found that nine sites did not store the injections in accordance with the recommended storage conditions (2°C–8°C). All the samples were transported and stored at 2°C–8°C at the FDA Laboratory prior to analysis. The products were tested using monographs in BP 2012 for oxytocin injection. Out of 185 samples, 112 (65.5%) failed either assay and/or sterility, including 2 falsified products. Out of the 169 oxytocin samples assayed, 94 (55.62%) failed in the content assay. The high failure rate for these uterotonics was attributed to (1) the proliferation of unregistered products, (2) absence of cold storage for a significant number of these products due to a lack of awareness of their appropriate storage conditions, and (3) dispensing of these products by facilities, like licensed chemical sellers, which are not authorized to sell medicines. The outcome of the project raised serious public health concerns (Karkari et al. 2012).

One possible strategy for extending access to stable oxytocin to healthcare centers is to store the drug under cold-chain conditions at regional drug depots and health facilities with reliable refrigeration (as used for vaccines), and then for community-based providers to maintain a smaller temporary supply outside the cold chain, only accessing the refrigerated stock periodically for resupply. For this approach to be successful, “Oxytocin-in-Uniject,” a product that incorporates time–temperature indicators (TTIs) has been developed. The TTI can change color in response to cumulative heat exposure; for example, the specific TTI for oxytocin was designed to reach the discard point at the equivalent of 17.2 days at 40°C, 72.5 days at 30°C, or 154 days at 25°C. Hence, providers can know the point at which an oxytocin injection should be discarded (Figure 4). An incremental cost analysis for maintaining the cold-chain and addition of TTI suggested a 3.5 fold increase in cost per dose (Tsu et al. 2003).

Figure 4. Temperature-time indicators (TTIs) for Oxytocin-in-Uniject product



Numerous studies have been conducted to characterize the distribution of time to discard these devices when stored under normal field conditions. In one study, devices manufactured in Argentina were transported (under refrigerated conditions) to study sites in Ghana, where these were kept under real life (unrefrigerated) conditions (Mullany et al. 2014). Over the simulation period, the ambient temperature at the site as well as the time to transition from usable to unusable product (as per TTI) were regularly recorded. In two simulation studies conducted, the median (range) time to discard was 43 (6 to 59) days and 33 (14 to 50) days, and the mean kinetic temperature exposure was 3.9°C higher in the second study. Simulating a monthly distribution system and assuming typical usage, product wastage under the proposed distribution model was predicted to be less than 10 percent.

A detailed survey was organized by the WHO PQT, in cooperation with the National Medicines Regulatory Authorities of 10 countries in Africa, Asia, and South America, to assess the quality of essential medicines available at the first level of the distribution channel. The scope of the study was very broad (covering 13 lifesaving commodities), and the details relevant to oxytocin injections are included in this summary. Of the 13 products tested, the highest proportion of noncompliant samples was found for oxytocin injection (64%). Samples of oxytocin injection (22 batches) produced by 15 manufacturers were assayed using the oxytocin injection monograph specified in International Pharmacopoeia. Among the 14 noncompliant batches, the oxytocin content was below the acceptance limit in 7 samples; in 2 batches, it was as low as 52.0 percent and 78.6 percent of the labeled amount. In six batches, the content of related substances was above the limit, suggesting the degradation of oxytocin and presence of degradation products (WHO 2015).

Recently, a systematic study was conducted to document the effect of temperature variations along the supply chain on the quality of oxytocin. For this study, 130 ampoules of oxytocin were shipped from the manufacturer in Germany to the service level in Ghana, and temperatures were recorded continuously. After 1 month of storage at the central, regional, and service levels, ampoules were sent to the laboratory for testing. The quality of the initial oxytocin sample from the manufacturer and the 130 oxytocin samples received from study points were tested according to the International Pharmacopeia monograph. All the samples complied with the specifications. The temperature profile showed that the lowest and highest temperatures experienced were −9.9°C and +30.1°C. The results suggest that the activity of oxytocin was not affected by these temperature excursions that occurred along the supply chain. The quality of oxytocin from the manufacturer, as well as from the service level, was within the required specifications (Kartoglu et al. 2017). The study details, methodology, and important results from some of the representative reports are summarized in Table 4.

The table suggests that LMICs often have poor-quality oxytocin injection. Possible reasons for this include (1) the product was out-of-specification when it was manufactured, (2) there is a lack of compliance with storage conditions leading to drug degradation, or (3) a combination of both. Kartoglu et al.'s (2017) recent results are surprising, but it is relevant to note that the product in this particular study was manufactured by a single manufacturer in Germany (which has strong medicines regulations) and were of good starting quality. A limitation of the study was the short storage time, which would not have been enough to induce significant degradation of oxytocin active ingredient in the formulation.

Table 4. Summary of Representative Reports on Quality and Stability of Oxytocin Injection Formulation in Markets

Study and Location	Sample Size	Analytical Method	Storage	Results	Major Limitation
Hogerzeil et al. 1993; Zimbabwe	Two batches each of 3 brands, 189 ampoules	Ph. Eur, Gradient HPLC	Dark 4-8°C and 30°C, Light at RT (21°C–25°C)	After 12 months at 30°C, 14% loss in potency; On refrigerated storage, no loss in potency	A robust study
De Groot et al. 1994; Netherlands	Tablet formulations	Isocratic HPLC method	Under various conditions	At 40°C/75% RH, 89% content after 14 weeks	Different formulation
Stanton et al. 2012; Ghana	46 ampoules purchased from market	BP, Gradient HPLC	In cold chain after purchase	26% within specifications	Limited sample size; quality of injection from supplier not known; uncontrolled storage conditions
Pribluda et al. 2012; Indonesia	110 ampoules from health offices and care centers	USP 2010	Not specified	88% within specifications	Quality of injection from supplier not known; uncontrolled storage conditions
Karkari et al. 2012; Ghana	169 ampoules manufactured in China, Pakistan and Belgium	BP, Gradient HPLC	Stored at 2°C–8°C	44% within specifications	Quality of injection from supplier not known; storage before sample collection not controlled
Stanton et al. 2014; India	193 ampoules purchased from market	USP # 33, Gradient HPLC	In cold chain after purchase	63% within specifications	Quality of injection from supplier not known; storage before sample collection not controlled
Mullany et al. 2014; Ghana	Two studies each of 550 packs of Oxytocin-in-Uniject manufactured in Argentina	TTI	Real-time conditions in rural settings	Product non-usable (based on TTI in current use) in 1st study: 6–59 days (temperature recorded 25.1°C–28.5°C); 2nd study: 14–50 days (temperature recorded 27.6°C–33.0°C)	Only TTI observed; oxytocin assay not conducted; too much variation in time for product non-usable to draw meaningful conclusion

Study and Location	Sample Size	Analytical Method	Storage	Results	Major Limitation
WHO 2015; Africa, Asia and South America	22 batches manufactured in 9 countries	Int P, Gradient HPLC	Stored either between 2°C and 8°C or at room temperature	36% within specifications	Quality of injection from supplier not known; storage before sample collection not controlled
Kartoglu et al. 2017; Ghana	130 ampoules from manufacturer (in Germany)	Int P , Gradient HPLC	In real time market for 1 month (between −9.9°C and +30.1°C)	100% within specifications	A robust study, though short storage time

6. Recommendations and Future Directions

Stability is defined as "the capacity of a drug product to remain within specifications established to ensure its identity, strength, quality, and purity" (FDA 1998). The purpose of a stability study is to characterize the degradation of a drug product and to establish an expiration dating period or shelf life applicable to all the batches of drug product. The FDA stability guidelines for new products indicate that a stability protocol should be established to describe not only how the stability study is to be designed and carried out, but also the statistical methods to be used for data analyses. Under current stability guidelines, FDA requires testing at least three batches, preferably more, to allow a reasonable estimation of the batch-to-batch variability, and to test the hypothesis that a single expiration dating period for all the batches is justifiable. Stability testing should be done at 3-month intervals during the first year, 6-month intervals during the second year, and annually thereafter. However, if the drug product is expected to degrade rapidly, more frequent sampling is necessary (Chow 2007).

Considering the above specifications, it is unfortunate that detailed and comprehensive stability data on oxytocin injection formulation are not available. A systematic approach is needed to ensure the availability of stable and effective oxytocin formulations. Some of the steps, which can be followed, are outlined below:

1. The results from various market survey reports have not been able to narrow down the actual cause of poor-quality oxytocin injections available in LMIC markets, which could be (a) manufacture of low-quality oxytocin in countries where regulations are not stringent, (b) exposure of product to high temperature for uncontrolled time periods during shipment and/or storage, or (c) a combination of the two. In view of this, a two-pronged approach may be necessary to ensure that quality oxytocin injections are made available to patients, including (a) stricter regulatory measures to ensure that the products meet specifications immediately after manufacture, and (b) storage specifications that align with the actual and real-life product use.

2. It is essential to validate pharmacopeial assay methods to establish their stability-indicating capability. The International Pharmacopeia has an impurity method for the injection and is assumed to be stability indicating.

3. Systematic stability studies, specifically for Climate Zone II and IV, in accordance with the ICH guidelines, should be conducted on representative generic products. The results from these studies can be used to reassess the specifications for storage and shelf life of oxytocin injection, on the basis of specific Climate Zone.

4. When comprehensive stability studies establish the instability of oxytocin injection in Climate Zone IV, innovative approaches can be taken to ensure that stable and effective formulations are available without delay, when needed. For example, researchers at the University of Monash, Australia, are investigating a prototype dry powder formulation with enhanced stability at elevated temperatures (up to 50°C) under "Inhaled Oxytocin Project." A sublingual oxytocin tablet is being developed, which would do away with the requirement for injection and would potentially offer better thermal stability. However, administration of oxytocin by any route other than injection is expected to be associated with a lag time, which may be life-threatening in compromised patients.

5. Considering the compromised solution-state stability of oxytocin in solution, another potential strategy is the concept of presenting the injection in Climate Zone IV as the lyophilized

form, to be reconstituted immediately before use. Lyophilization is a popularly used drying technique, when the API is not sufficiently stable in solution state to meet shelf-life requirements. Right before use, the lyophilized powder can be reconstituted with water or suitable diluent. Undoubtedly, such a strategy would lead to an increase in the product cost, but the stability of the dried formulation in extreme weather conditions would be ensured. The lyophilized injection, formulated to be stable in Climate Zone IV, can potentially lead to an extended shelf-life, hence cancelling out the influence of increased manufacturing cost.

Oxytocin injection products labeled with a shelf life of 3 years are available in regions where the average temperature from April to September is 30°C, such as Delhi, India (data from weather report on line, World Weather online). This can potentially be a serious problem. For oxytocin, it would be appropriate to reappraise the current shelf life and storage specifications (including temperature requirements) with a view to optimizing effectiveness, safety, and product accessibility (Hodgins and Lukulay 2017).

7. Conclusion

WHO recommends oxytocin as the first-line drug for the prevention and treatment of postpartum hemorrhage. In spite of the established efficacy of the drug, the limited access of the formulation, specifically in developing countries, is a serious concern. This may be attributed to the compromised stability of the drug in aqueous injections, because of inappropriate storage. We have presented various literature reports demonstrating unregulated storage conditions in resource-limited countries to be the probable cause of compromising the stability of oxytocin. A stability study to establish the shelf-life of oxytocin formulation in Climate Zone IV conditions still needs to be conducted. Alternative formulation strategies can be explored to ensure the availability of stable and effective oxytocin formulations to prevent treatment failure and ultimately improve maternal health.

Annex 1: Case Study of a Similar Product

The stability problem encountered with levothyroxine sodium can serve as a good learning tool. Levothyroxine sodium formulations were first introduced in the market before 1962, and the assay method was based on iodine content. Using the HPLC method, there have been numerous reports indicating problems with the stability of oral levothyroxine sodium products. As a result, in 1982 FDA organized a workshop in conjunction with USP to set the standard for the use of stability-indicating HPLC assay for quality control of the drug product (Garnick et al. 1982). In addition to raising concerns about the consistent potency of orally administered levothyroxine sodium products, many reports suggested that the customary 2-year shelf life may not be appropriate for these products. Levothyroxine sodium exhibited a biphasic first-order degradation profile with an initial fast degradation followed by a slower rate (Won 1992). To compensate for the initial accelerated degradation, some pharmaceutical companies use an overage of active ingredient in their formulation, which can lead to occasional instances of superpotency.

Table A1. Comparison of Acetic Acid and Water Content Specifications for Oxytocin API, as Recommended by Different Pharmacopoeias

	Acetic Acid Content	Water Content
USP 40	6.0% to 10.0%	*(Note: monograph is silent on water content)*
EP, 9th Edition*	6.0% to 10.0%	NMT 5.0% determined on at least 50 mg^2
Int P 2016 6th Edition	NLT 60 mg/g and NMT 100 mg/g	NMT 50 mg/g
BP 2018	6.0% to 10.0%	NMT 5.0% on at least 50 mg
JP 17th Edn, 2016	6.0% to 10.0%	NMT 5.0%, coulometric titration
Indian Pharmacopoeia 2014	*(Note: monograph is silent on acetic acid content)*	*(Note: monograph is silent on water content)*
Indian Pharmacopoeia 2018	*(Note: monograph is silent on acetic acid content)*	*(Note: monograph is silent on water content)*

* EP does not have Oxytocin Injection monograph, it has Oxytocin Concentrated Solution monograph. BP allows preparation of Oxytocin injection from Oxytocin and Oxytocin Concentrated Solution

Table A2. Comparison of Identification and Assay Methods for Oxytocin API and FPP, as Recommended by Different Pharmacopoeias

	Identification		Assay	
	API	FPP	API	FPP
USP 40	RT– HPLC and either (NMR or Amino Acid Test)	*(Note: monograph is silent on identification requirement)* †	HPLC – calculate potency, its oxytocic activity is NLT 400 USP Oxytocin Units per mg	HPLC– calculate potency, 90.0% to 100.0%
EP, 9th Edition*	2 tests: A) ID by RT – HPLC and Amino Acid analysis	RT by HPLC, amino acid analysis	HPLC – calculate content of oxytocin 93.0% to 102.0%	HPLC – calculate content of oxytocin peptide, 95.0%–105.0%
Int P 2016 6th Edition	ID by IR and either 2 of the following: TLC; RT –HPLC; UV absorbance with maxima at 275nm and absorptivity of 14-16 Complies with Amino Acids analysis	Perform either TLC or RT – HPLC	HPLC– calculate content of oxytocin peptide: 93.0% to 103.0%	HPLC – calculate content of oxytocin 90.0% to 110.0%
BP 2018	ID by RT – HPLC and Amino acid analysis	2 tests: TLC and RT – HPLC	HPLC – calculate the content of oxytocin: 93.0% to 102.0%	HPLC – calculate the content of oxytocin: 90.0% to 110.0%
JP 17th Edn, 2016	ID by UV. Complies with Constituent amino acids.	(Note: monograph is silent on identification requirement) †	HPLC – NLT 540 and NMT 600 oxytocin Units per mg	HPLC – 90.0% to 110.0% of the labeled oxytocin Units
Indian Pharmacopoeia 2014	3 tests: A) ID by RT – HPLC; B) Amino acid analysis, and C) biological response Test B may be omitted if tests A and C are carried out. Test C may be omitted is tests A and B are carried out	ID by RT – HPLC	HPLC – Peptide: 90.0% to 110.0% of the stated amount of oxytocin, expressed per mg for the solid, and in mg per mL for the liquid calculate the units of oxytocic activity or The potency; if from animal, NLT 95.0% and NMT 105.0% and if synthetic NLT 560 Units per mg, if liquid, NLT 150 Units per mL	HPLC – NLT 90.0% and NMT 110.0% of the stated number of Units of oxytocin activity

	Identification		Assay	
	API	FPP	API	FPP
Indian Pharmacopoeia 2018	3 tests: A) ID by RT – HPLC; B) Amino acid analysis, and C) biological response Test B may be omitted if tests A and C are carried out. Test C may be omitted is tests A and B are carried out	ID by RT – HPLC	HPLC – Peptide: 90.0% to 110.0% of the stated amount of oxytocin, expressed per mg for the solid, and in mg per mL for the liquid calculate the units of oxytocic activity or The potency; if from animal, NLT 95.0% and NMT 105.0% and if synthetic NLT 560 Units per mg, if liquid, NLT 150 Units per mL	HPLC – NLT 90.0% and NMT 110.0% of the stated number of Units of oxytocin activity

Footnote: Note that RT – HPLC: ID by Retention Time from HPLC procedure

* EP does not have Oxytocin Injection monograph, it has Oxytocin Concentrated Solution monograph. BP allows preparation of Oxytocin injection from Oxytocin and Oxytocin Concentrated Solution

† USP and JP require system suitability tests requiring resolution of oxytocin peak from related substance and repeatability tests of the oxytocin peak identified by retention time match.

Table A3. Comparison of Related Substance, Sterility, and Limits for Endotoxin for Oxytocin API and FPP, as Recommended by Different Pharmacopoeias

	Related Substances		Sterility		Limit for Endotoxin	
	API	FPP	API	FPP	API	FPP
USP 40	Sum of responses from impurities not more than 5% of the area of the oxytocin peak.	(*Note: Monograph is silent on Related Substances)*	*(Note: monograph is silent on sterility* - total bacterial count does not exceed 200 cfu per g. For animal origin products, it meets requirement for absence of *Salmonella* and *Escherichia coli.)*	Oxytocin injection is s sterile solution of Oxytocin in a suitable diluent	*(Note: monograph is silent on Endotoxin)* Microbial enumeration test <61>, <62>, tests for absence of *Salmonella* species and *Escherichia Coli*.)	Not more than 35.7 Endotoxin Units per USP Oxytocin Unit.
EP, 9th Edition*	Any impurity ≤ 1.5 %; Total ≤ 5 %; Disregard limit: 0.1 %	Any impurity ≤ 1.5 %; Total ≤ 5 %; Disregard limit: 0.1 %	*(Note: Sterility not required;* If the substance is sterile, store in a sterile, airtight, tamper-proof container)	If the substance is sterile, store in a sterile, airtight, tamper-proof container	Less than 300 IU in volume that contains 1mg of oxytocin	Less than 300 IU in volume that contains 1mg of oxytocin
Int P 2016 6th Edition	Any impurity ≤ 1.5 % Total ≤ 5 % Disregard limit <0.1%	The area of NMT one impurity peak is >2%. No impurity peak is >5%	*(Note: Sterility not required,* if sterile, package appropriately)	Oxytocin injection is a sterile solution of oxytocin in a suitable diluent	Less than 300 IU/mg	Less than 0.5 IU of endotoxin per IU of oxytocin
BP 2018	Any impurity ≤ 1.5 % Total ≤ 5 % Disregard limit 0.1%	*Note: Monograph is silent on Related Substances)*	*(Note: Sterility not required:* If the substance is sterile, store in a sterile, airtight, tamper-proof container	Oxytocin Injection is a sterile solution of oxytocin or a sterile dilution of Oxytocin Concentrated Solution in water for injections	Less than 300 IU/mg	*Complies with Test for Endotoxins under Parenteral Requirements*

	Related Substances		Sterility		Limit for Endotoxin	
	API	FPP	API	FPP	API	FPP
JP 17th Edn, 2016	The amount of each peak other than Oxytocin is NMT 1.5% and the total of them is not more than 5.0%	*(Note: monograph silent on related substances or purity requirements)*	*(Note: monograph is Silent)*	Sterility: it meets the requirement	Less than 10 EU/oxytocin Unit	Less than 10 EU/oxytocin Unit
Indian Pharmacopoeia 2014	*(Note: monograph is silent on related substances requirements)*	*(Note: monograph is silent on related substances requirements)*	Complies with test for sterility	Oxytocin Injection is a Sterile solution in Water for Injection	Not more than 0. Endotoxin Units per Unit of oxytocin	Not more than 0.5 Endotoxin Units per Unit of oxytocin
Indian Pharmacopoeia 2018	*(Note: monograph is silent on related substances requirements)*	*(Note: monograph is silent on related substances requirements)*	Complies with test for sterility	Oxytocin Injection is a Sterile solution in Water for Injection	Not more than 0. Endotoxin Units per Unit of oxytocin	Not more than 0.5 Endotoxin Units per Unit of oxytocin

* EP does not have Oxytocin Injection monograph, it has Oxytocin Concentrated Solution monograph. BP allows preparation of Oxytocin injection from Oxytocin and Oxytocin Concentrated Solution

Table A4. Comparison of Other Tests and Packaging Specifications for Oxytocin API and FPP, as Recommended by Different Pharmacopoeias

	Other Tests	Additional information	Other Tests	Packaging	
	API	API	FPP	API	FPP
USP 40	(Note: Monograph is silent on appearance or optical rotation)	(no solubility info)	Complies with USP <1> Injections and Implanted Drug Products; Particulate matter in Injections	Preserve in tight containers, preferably of Type I glass	Preserve in single-dose or multiple-dose containers, preferably of Type I glass or in suitable plastic containers.
EP, 9th Edn*	Appearance: white or almost white, hygroscopic powder--	Very soluble in water Dissolves in dilute solutions of acetic acid and ethanol	Complies with General Chapter on Pharmaceutical Preparations,	In an airtight container, protected from light, If the substance is sterile, store in a sterile, airtight, tamper-proof container	Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container
Int P 2016 6th Edition	Specific optical o rotation of 5 mg/mL solution is -24.0° to -28.0°	Very Soluble in water Soluble in dilute acetic acid and ethanol	Oxytocin injection complies with the general chapter for Parenteral preparations	Oxytocin should be kept in an airtight container, protected from light. Or if sterile, in a sterile, airtight, tamper-evident container.	Oxytocin injection should be kept protected from light. The manufacturer may provide additional information on the label regarding storage conditions for a specified period which may differ from the long-term storage conditions.
BP 2018	Appearance: White or almost white, hygroscopic powder	Very soluble in water It dissolves in dilute solutions of acetic acid and ethanol (96%)	"The injection complies with the requirements stated under Parenteral Preparations and with the following requirements" Characteristics: A clear, colorless liquid	Store in an airtight container. If the substance is sterile, airtight, tamper-proof container	Complies Parenteral Preparation Storage: in a sterile, airtight, tamper-proof container

	Other Tests	Additional information	Other Tests	Packaging	
	API	API	FPP	API	FPP
JP 17th Edn, 2016	(Note: monograph is silent on appearance or specific rotation)	Very Soluble in water Freely soluble in ethanol (99.5%) Dissolves in HCL TS	Meets the requirements: Extractable volume Foreign Insoluble matter Insoluble particulate matter	Containers-Tight containers	Containers-Hermetic containers
Indian Pharmacopoeia 2014	Appearance: when presented as solid, a white or almost white powder. When presented as liquid, a clear colorless liquid	Soluble in water, 1-butanol, and 2-butanol	Complies with the tests under: Parenteral Preparations (Injections) Vasopressin Impurity: NMT 0.5 Unit per mL Purity: the RSD of the ratio of the peak area that of the internal standard is NMT 2.0%	Store protected from moisture. If the substance is intended for use in the manufacture of parenteral preparations, the container should be sterile, tamper-evident, and sealed so as to exclude micro-organisms	(monograph is silent on packaging)
Indian Pharmacopoeia 2014	Appearance: when presented as solid, a white or almost white powder. When presented as liquid, a clear colorless liquid		Complies with the tests under: Parenteral Preparations (Injections) Vasopressin Impurity: NMT 0.5 Unit per mL Purity: the RSD of the ratio of the peak area that of the internal standard is NMT 2.0%	Store protected from moisture. If the substance is intended for use in the manufacture of parenteral preparations, the container should be sterile, tamper-evident, and sealed so as to exclude micro-organisms	(monograph is silent on packaging)

* EP does not have oxytocin injection monograph, it has oxytocin concentrated solution monograph. BP: oxytocin injection is a sterile solution of oxytocin or a sterile dilution of oxytocin concentrated solution in water for injections.

Table A5. Comparison of Additional API Label Details, as Recommended by Different Pharmacopoeias

	Mol. Wt.	Formula	Label Claim and Units	Criteria	Basis	Source	Other
USP 40	1007.17 [50-56-6]	C43H66N12O12S2	Its oxytocic activity is NLT 400 USP Oxytocin Units per mg	NLT 400 USP Oxytocin limits	As is	synthetic	
EP, 9th Edition*	1007 [50-56-6]	C43H66N12O12S2	93.0% to 102.0% 1 mg of oxytocin peptide is equivalent to 600 IU of biological activity	93.0% to 102.0%	anhydrous and acetic-free substance	synthetic	
Int P 2016 6th Edition	1007	C43H66N12O12S2	93.0% to 103.0% of the peptide 1 mg of oxytocin peptide is equivalent to 600 IU of biological activity	93.0% to 103.0%	calculated on the anhydrous and acetic acid-free substance	synthetic	Available in freeze-dried form as an acetate
BP 2018	1007	C43H66N12O12S2	93.0% to 102.0% 1 mg of oxytocin peptide is equivalent to 600 IU of biological activity	93.0% to 102.0%	calculated on the anhydrous and acetic acid-free substance	synthetic	Available in freeze-dried form as an acetate
JP 17th Edn, 2016	1007.19 [50-56-6]	C43H66N12O12S2	It contains NLT 540 oxytocin Units and NMT 600 oxytocin Units per mL,	NLT 540 oxytocin Units and NMT 600	calculated on the anhydrous and residual acid-free substance	synthetic	
Indian Pharmacopoeia 2014	1007.2	C43H66N12O12S2	If derived from animal, Oxytocin contains NLT 95.0% and NMT 105.0% of stated numbers of Units of oxytocic activity If synthetic solid, it contains NLT 560 Units per mg; if synthetic liquid, it contains NLT 150 Units per mL	Animal: 95.0%–105.0%; synthetic solid: NLT 560 Units per mg; synthetic liquid: NLT 150 Units per mL	Synthetic is calculated with reference to the peptide content	Animal or synthetic	

	Mol. Wt.	Formula	Label Claim and Units	Criteria	Basis	Source	Other
Indian Pharmacopoeia 2018	1007.2	C43H66N12O12S2	If derived from animal, Oxytocin contains NLT 95.0% and NMT 105.0% of stated numbers of Units of oxytocic activity If synthetic solid, it contains NLT 560 Units per mg; if synthetic liquid, it contains NLT 150 Units per mL	Animal: 95.0%–105.0%; synthetic solid: NLT 560 Units per mg; synthetic liquid: NLT 150 Units per mL	Synthetic is calculated with reference to the peptide content	Animal or synthetic	

* EP does not have a monograph for oxytocin injection, but does have an oxytocin concentrated solution monograph. BP allows preparation of oxytocin injection from oxytocin and oxytocin concentrated solution.

Table A6. Comparison of Additional FPP Label Details, as Recommended by Different Pharmacopoeias

	Acceptance Criteria Definition	Units
USP 40	Each mL possesses oxytocic activity NLT 90.0% and NMT 110.0% of Label in USP Oxytocin Units	90.0 to 110.0%
EP, 9th Edition*	95.0% to 105% of peptide stated per mL	95.0 to 105.0%
Int P 2016 6th Edition	The label states the IU per mL and oxytocin peptide content in mg per mL. Definition: NLT 90.0% and NMT 110.0%	90.0 to 110.0%
BP 2018	The label states the strength as the number of UN (Units) per mL. The label also states the equivalent number of microgram of oxytocin per mL. Definition: 90.0% to 110.0% of the stated amount of the peptide, g of oxytocin per mL	90.0 to 110.0%
JP 17th Edn, 2016	It contains NLT 90.0and NMT 110.0% of the labeled oxytocin Units	90.0 to 110.0%
Indian Pharmacopoeia 2014	The label states (1) the number of Units of oxytocin activity per mL; 2) either the animal species from which is obtained or whether it is synthetic, as appropriate Contains NLT 90.0% and NMT 110.0% of the stated number of Units of oxytocin activity	90.0 to 110.0%
Indian Pharmacopoeia 2018	The label states 1) the number of Units of oxytocin activity per mL; 2) either the animal species from which is obtained or whether it is synthetic, as appropriate Contains NLT 90.0% and NMT 110.0% of the stated number of Units of oxytocin activity	90.0 to 110.0%

* EP does not have a monograph for oxytocin injection, but does have an oxytocin concentrated solution monograph. BP allows preparation of oxytocin injection from oxytocin and oxytocin concentrated solution.

Additional Notes

For the API, all pharmacopeias use a similar method for the API assay (220 nm, C18 column (L1), gradient)

For the FPP the methods are different. Two of the pharmacopeias (BP and IP) use an isocratic method and the other three (USP, JP, IP) are gradient methods

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