

Oxytocin Injection Job Aid to Assist with Dossier Preparation

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Acronyms

API	active pharmaceutical ingredient
BP	British Pharmacopeia
CTD	common technical document
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPP	finished pharmaceutical product
HPLC	high-performance liquid chromatography
IDA	International Dispensary Association
Int. Ph.	International Pharmacopeia
JP	Japanese Pharmacopeia
NMT	no more than
PF	pharmaceutical forum
Ph. Eur.	European Pharmacopeia
PQM+	Promoting the Quality of Medicines Plus
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Overview

This document is a job aid to enable quick access to technical information by those preparing dossiers for oxytocin. The information consists of guidance on stability, storage, and controls. The information herein is adapted from the Promoting the Quality of Medicines report “Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review” (July 2018).

Aid for CTD Module 2.3.P.5 – Control of Drug Product

Table 1. Stability-Indicating Methods

Method	Elution/Eluent	Stability Indicating
HPLC: Chaibva and Walker, J Pharm Biomed Anal. 2007; 43:179–85 Krummen and Frei, J Chromatogr, 1977; 132, 429 O'Hare and Nice J Chromatogr A., 1979;171:209-26	Isocratic/ acetonitrile and phosphate buffer	Yes
HPLC: USP EP	Gradient/ phosphate buffer and acetonitrile as mobile phases	Not mentioned

Aid for CTD Module 2.3.P.2 – Oxytocin Formulation Development

Table 2. Oxytocin Injection Formulation

Substance	Content
Container sizes	<ul style="list-style-type: none"> • 1 mL ampoules • 1 mL disposable syringes • 1 mL and 10 mL vials
Formulation	<ul style="list-style-type: none"> • 10 units/mL • 0.5% chlorobutanol v/v • Syntocinon (Novartis) contains 0.61% v/v • Acetic acid for pH adjustment
Excipients	<ul style="list-style-type: none"> • Acetic acid (glacial) • Sodium acetate trihydrate • Sodium chloride • Sodium hydroxide • Water for injection

Aid for CTD Module 2.3.P.3 – Oxytocin Manufacture

Table 3. Injection Formulations of Oxytocin Approved by 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; 100 IU/10 mL 300 IU/30 mL
	018261	Par Sterile Products	Pitocin	10 IU/mL; 100 IU/10 mL 500 IU/50 mL

Regulatory Body	Reference Number	Applicant	Status	Dosage Available
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

Aid for CTD Module 2.3.P.8 – Stability for Oxytocin

Table 4. General Control of Oxytocin Stability

CQA Parameter	Specification for control
pH	<ul style="list-style-type: none"> Drug product controlled at release (see table “Storage, Labeling, and pH Specification by Pharmacopeia”)
Storage Temperature	<ul style="list-style-type: none"> 2-8° C recommended NMT 30° C for 1 month NMT 40° C for 1 week

Table 5. Storage, Labeling, and pH Specifications by Pharmacopeia

	Storage Temperature		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 Ed.‡	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†
Ph. Int. 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

	Storage Temperature		Labeling		pH	
	API	FPP	API	FPP	API	FPP
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 Ed, 2016	2°C–8°C	Cold place (1°C–15°C) and avoid freezing.	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) if contents are 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 an oxytocin injection monograph, it has an 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, must be shown on the immediate container or wrapping of them, JP XVII.

Table 6. WHO/IDA Stability Study: Two Batches of Three Brands of Oxytocin Ampoules

Storage Temperature	Shelf Life
2°C -8C°	3 years
<21 °C	2 years
25 °C	1 year
30 °C	6 months
40 °C	1 week

Table 7. Recommended Storage and Shelf Life of Products, with Country of Manufacture (WHO 2015)

S. No.	Name of Manufacturer	Country of Manufacture	Country of Collection	Recommended Storage	Shelf-Life
1	Zhejiang Tianfeng Pharmaceutica	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 Arzneimittelwerk	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

References

Promoting the Quality of Medicines. "Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review" [July 2018] Available from:
<https://www.usp-pqm.org/sites/default/files/pgms/article/stability-storage-oxytocin-jul2018.pdf>