MODULE III

MISOPROSTOL

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Manual for Procurement & Supply of
Quality-Assured MNCH Commodities

MISOPROSTOL

TABLETS, 200 MICROGRAMS

GENERAL PRODUCT INFORMATION

Misoprostol is a synthetic analog of a natural prostaglandin E1. It has been widely approved for treatment and prevention of peptic ulcer disease for over a decade before it was investigated as a uterotonic and oxytocic agent. As a result, misoprostol is currently used for two distinct purposes:

- Gastroprotection and healing of peptic and duodenal ulcers
- A variety of obstetric and gynecological indications, including medical abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and prevention and treatment of PPH

Misoprostol is considered an essential medicine by the UN Commission on Life-Saving Commodities for its PPH indication because PPH is the leading cause of maternal death. This document therefore focuses on misoprostol for its use in PPH only.

The WHO's Essential Medicine List (EML) recommends using misoprostol for preventing and treating PPH when oxytocin is unavailable or cannot be administered safely. Although oxytocin injection is the preferred first-line medicine for the prevention and treatment of PPH, the major limitations of oxytocin are that it requires a cold chain and skilled administration to deliver effective results. These two conditions cannot always be met in low-resource settings. Misoprostol does not need to be stored in the cold chain and its simple tablet form facilitates its use by community health workers and traditional birth attendants. The drug's ease of use and stability at room temperature make it suitable for delivery in low-resource settings. It is therefore recommended as an alternative to oxytocin in the prevention and treatment of PPH where oxytocin use is not feasible or safe.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

2. The procurer must obtain evidence of the quality, and in particular, the stability of product from the manufacturer before ordering as the use of inappropriate excipients or inadequately controlled environmental conditions can also increase exposure to moisture and cause product degradation. Pre-shipment testing is pointless for inappropriately manufactured and packaged product—the product may comply with specifications shortly after manufacturing but may only have 50 percent of labeled content within six months.

KEY QUALITY CONSIDERATIONS

Product specification

Misoprostol finished product must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

The packaging requirement for misoprostol is double-aluminum blister packs. Packaging is critical for the stability of misoprostol; double-aluminum blister packs effectively protect the products from moisture and prevent degradation.

Products presented in PVC or PVDC/aluminum blister packs should never be purchased because PVC or PVDC/aluminum do not provide adequate protection against penetration by moisture.

When procuring SRA-approved products, the suitability of packaging for the intended markets should be reassessed. For example, some misoprostol products approved in SRA markets (climatic zone II) are packaged in plastic bottles, which is not suitable for use in countries in climatic zones III and IV with high temperature and humidity.

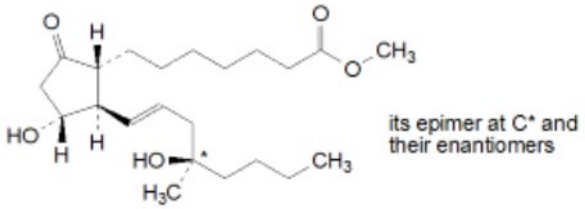
Procurers should ensure that package inserts of the products eligible for procurement include information on the PPH indications and dosages. Misoprostol has a variety of obstetric and gynecological indications, including PPH. However, only a few products are registered for those indications. Many misoprostol products are registered for gastric ulcer uses and manufacturers' package inserts do not provide information specific for the PPH indication.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablet form.

Additional information about the misoprostol finished product storage requirement can be found in the "Storage, Stability and Degradation" section below.

Name of the Medicinal Product	Misoprostol
Chemical Name	(±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate
Chemical Structure	$C_{22}H_{38}O_5$ 
Pharmaceutical Form	For use in the prevention and treatment of PPH, misoprostol is available in an oral tablet form, which can be administered orally or sublingually.
Qualitative and Quantitative Composition	Each tablet contains 200 micrograms (mcg) of misoprostol. List of excipients[1]: – Microcrystalline cellulose – Hydrogenated castor oil – Sodium starch glycolate – Hypromellose
Packaging and Presentation	Typically, cold-form double-aluminum blister (Alu/Alu) is used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

[1] Based on the formulation of an innovator product, Cytotec®.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of February 2018, there are three misoprostol 200 mcg tablets prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at: https://extranet.who.int/prequal/content/prequalified-lists/medicines.

Table M-1. WHO-Prequalified Misoprostol 200 mcg Tablets

WHO REF.	MARKETING AUTHORIZATION	MANUFACTURING SITE	DOSAGE FORM AND	PACKAGING AND	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH039	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	FPP manufacturing site: Cipla Ltd, Unit 8, Plot No. L-139 to L-147-1, S-103 to S-105, S-107 to S-112 and M-61 to M-63, Verna Industrial Estate, Salcette, Goa, 403 722, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 4x1, 4x7, 4x15	8-Apr-14	2 years	Do not store above 30°C.
RH048*	China Resources Zizhu Pharmaceutical Co Ltd, No 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China	FPP manufacturing site: China Resources Zizhu Pharmaceutical Co Ltd, No. 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 3x1, 4x1	22-Nov-16	2 years	Do not store above 30°C.
RH056*	Acme Formulation Pvt. Limited, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India	FPP manufacturing site: Acme Formulation Pvt. Ltd, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 10x10	27-Apr-16	2 years	Do not store above 30°C; protect from light.

** Include the indication for PPH*

Table M-2. Examples of SRA-Approved Misoprostol 200 mcg Tablets

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Cytotec 200 mcg tablets*	UK MHRA	Pfizer Limited	PL 00057/0956	Oral tablet; cold-formed aluminum blister pack	3 years	Do not store above 30°C. Store in the original package to protect from moisture.
Cytotec*	US FDA	GD Searle LLC, Division of Pfizer Inc	NDA #019268	Oral tablet; bottle	Not specified	Store at or below 25°C, in a dry area.
Misoprostol *	US FDA	Ivax Sub Teva Pharms	ANDA #076095	Oral tablet; bottle	Not specified	Store at 20°–25°C in a dry area. [See USP controlled room temperature.]
Misoprostol *	US FDA	Novel Lab Inc.	ANDA #091667	Oral tablet; bottle	Not specified	Store at 20–25°C. [See USP controlled room temperature.] Store in a dry area.

** Registration for gastrointestinal indications.*

*** Registration for the indications of medical interruption of intrauterine pregnancy, in combination with mifepristone; and preparation of the cervix before surgical interruption of pregnancy during the first trimester.*

**** Registration for the indication of medical termination of a developing intrauterine pregnancy, in sequential combination with mifepristone.*

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Cytotec 200 mcg, comprimé sécable*	ANSM, France	Pfizer Holding France	34009 328 785 8 1,	Oral tablet;	3 years	Not specified
			34009 328 786 4 2	bottle (amber glass), blister pack (PE/PVC/		
GyMiso 200 mcg, comprimé**	ANSM, France	Linepharma, France	34009 362 499 4 3	Oral tablet;	2 years	Store at a temperature not exceeding 25°C
				blister pack (paper/PE/		
Cytotec tablets (misoprostol 200 mcg)*	Swissmedic	Pfizer PFE Switzerland, GmbH	46945	Oral tablets;	Not specified	Store at room temperature (15-25°C).
				not specified		
Cytotec misoprostol 200 mcg tablet blister pack*	TGA Australia	Pfizer Australia Pty Ltd	AUST R 63983	Oral tablet;	3 years	Store below 25°C; protect from moisture.
				cold formed Alu/Alu blister pack		
Cytotec misoprostol 200 mcg tablet bottle—EX (export only)*	TGA Australia	Proqualix Pty Ltd (in administration)	AUST R 46849	Oral tablet;	Not specified	Not specified
				bottle		
GyMiso misoprostol 200 mcg oral tablet blister pack***	TGA Australia	MS Health Pty Ltd	AUST R 188015	Oral tablet;	2 years	Store below 25°C in the original packaging.
				Alu/Alu blister pack		

** Registration for gastrointestinal indications.*

*** Registration for the indications of medical interruption of intrauterine pregnancy, in combination with mifepristone; and preparation of the cervix before surgical interruption of pregnancy during the first trimester.*

**** Registration for the indication of medical termination of a developing intrauterine pregnancy, in sequential combination with mifepristone.*

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other formulations of misoprostol that exist in the market include the following products.

Vaginal tablet 25 mcg	Included in the WHO EML, only for use for induction of labor where appropriate facilities are available
Misoprostol oral tablet 100 mcg	Indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer; for example, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer
Misoprostol oral tablet 400 mcg (e.g., Topogyne®, Misoone®)	Indicated for medical termination of developing intrauterine pregnancy, in sequential use with mifepristone
Misoprostol vaginal 200 mcg vaginal delivery system (e.g., Mysodelle®, Misodel®)	A controlled release formulation that releases misoprostol at a rate of approximately 7 micrograms/hour over a period of 24 hours Indicated for induction of labor in women with an unfavorable cervix, from 36 weeks gestation, in whom induction is clinically indicated

Combination pack of mifepristone and misoprostol (e.g., Medabon®)	Included in the WHO EML, only for use for medical abortion where permitted under national law and where culturally acceptable Consists of 1 tablet of mifepristone 200 mg tablet and 4 tablets of misoprostol 200 mcg tablet

It is important to note that for the PPH indication the WHO EML recommends the use of misoprostol 200 mcg tablets for convenient use in accordance with the dosing regimens. WHO recommends 600 mcg orally for the prevention of PPH, and sublingual misoprostol at 800 mcg for controlling PPH when oxytocin is unavailable.

STORAGE, STABILITY, AND DEGRADATION

Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablets.

Misoprostol turns into three main inactive degradation products: type A, type B, and 8-epimer misoprostol. The inactive type A misoprostol occurs by dehydration, which produces water. The 8-epi misoprostol is obtained by isomerization. These degradation processes are catalyzed by the presence of water. The type B misoprostol is the result of isomerization of the inactive type A. The rate of degradation increases as water content increases.

It is therefore important to exclude water (moisture) at all stages of the manufacturing process and during storage of the product to ensure that the product will be stable throughout its shelf life. Critical factors related to exclusion of moisture include:

- Selection of API
- Selection of excipients
- Production environment (temperature and relative humidity)
- Packaging

Packaging is very important for the stability of misoprostol. A study of the quality of misoprostol sampled in the field[2] has shown that misoprostol tablets packaged in PVC-aluminum blisters are likely to degrade more rapidly than those packaged in aluminum-aluminum blisters, especially under conditions of high temperature and humidity.

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Therefore, misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

[2] World Health Organization. 2016. "Quality of Misoprostol Products." In: *WHO Drug Information.* Vol. 30, No. 1. Geneva: WHO. Available at http://www.who.int/medicines/publications/druginformation/WHO_DI_30-1_Quality.pdf

Storage condition: Do not store above 30˚C.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in the table in this module's Sections 2.1 and 2.2, respectively.

PRODUCT SPECIFICATIONS

The product must meet the International Pharmacopoeia specifications,[3] or the equivalent thereof.

International Pharmacopoeia

Table M-3. International Pharmacopoeia Specifications for Misoprostol

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification* a) HPLC	The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).	1.14.4 High-performance liquid chromatography
Identification* b) TLC	The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).	1.14.1 Thin-layer chromatography
Dissolution	The amount in solution is not less than (NLT) 80% (Q) of the amount declared on the label.	5.5 Dissolution test for solid oral dosage forms
Related substances**	In the chromatogram obtained with solution (1): – The sum of the areas of any peak corresponding to impurity A, B, and E is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%). – The area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%). – The area of any peak corresponding to impurity D is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).	1.14.4 High-performance liquid chromatography
Assay***	90.0–110.0%	1.14.4 High-performance liquid chromatography
Uniformity of content	Each single unit contains within ±15% of the average amount of the active ingredient. However, if one individual unit deviates by more than ±15% but is within ±25% of the average amount of the active ingredient,	5.1 Uniformity of content for single-dose preparations

[3] As of February 2018, there are no monographs of misoprostol tablets published in the US or British Pharmacopoeia; please check for updated information.

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	examine a further 20 units drawn from the same original sample as the first 10 units. The preparation under test complies only if the amount of active ingredient found in no more than one out of 30 units deviates by more than ±15% of the average amount. None deviates by more than ±25% of the average amount.	

** Either test A or B may be applied.*

*** Impurity A = 8-epi-misoprostol*
Impurity B = 12-epi-misoprostol
Impurity C = misoprostol A
Impurity D = misoprostol B
Impurity E = Methyl rac-(13E,16RS)-11α,16-dihydroxy-16,18-dimethyl-9-oxo-20-norprosta-13,17-dien-1-oate (mixture of 4 stereoisomers)

**** It is acceptable to use the average of the 10 individual results obtained in the test for "uniformity of content."*

MISOPROSTOL ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Misoprostol is used for a variety of obstetric and gynecological indications:

- Prevention and treatment of PPH where oxytocin is not available or cannot be safely used.
- Management of incomplete abortion and miscarriage.
- First-trimester abortion: misoprostol in combination with mifepristone is indicated for the medical termination of intrauterine pregnancy. The duration of pregnancy for which the product is approved may be different in different countries.
- Cervical ripening: cervical ripening prior to uterine instrumentation; cervical ripening for induction of labor in case of a live fetus and intrauterine fetal death.

It is also indicated for gastroprotection and healing of peptic and duodenal ulcers.

Posology, method, and duration of administration

Posology, Method and Duration of Administration for Misoprostol

INDICATION	DOSAGE	NOTES
PPH prevention	600 mcg orally single dose	– Included in the WHO EML. – Exclude second twin before administration.
PPH treatment	800 mcg sublingually single-dose	
Incomplete abortion (first trimester)	600 mcg orally single-dose or 400 mcg sublingually single-dose	– Included in the WHO EML. – Leave to work for 1–2 weeks (unless there is heavy bleeding or infection).
Missed abortion (first trimester)	800 mcg vaginally 3-hourly (max x2) or 600 mcg sublingual 3-hourly (max x2)	– Give 2 doses and leave to work for 1–2 weeks (unless there is heavy bleeding or infection).
Induced abortion (first trimester)	800 mcg vaginally 3-hourly (max x3 within 12 hours) or 800 mcg sublingually 3-hourly (max x3 within 12 hours)	– Ideally used 48 hours after mifepristone 200 mg.
Induced abortion (second trimester)	400 mcg vaginally 3-hourly (max x5) or 400 mcg sublingually 3-hourly (max x5)	– Most effective when used 48 hours after mifepristone 200 mg.

INDICATION	DOSAGE	NOTES
Intrauterine fetal death (second trimester)	13–17 weeks: 200 mcg vaginally 6-hourly (max x4) 18–26 weeks: 100 mcg vaginally 6-hourly (max x4) 27–43 weeks: 25-50 mcg 4-hourly	– Halve dose in women with previous cesarean section.
Intrauterine fetal death (third trimester)	25 mcg vaginally 6-hourly or 25 mcg orally 2-hourly	– Reduce doses in women with previous cesarean section.
Induction of labor (third trimester)	25 mcg vaginally 6-hourly or 25 mcg orally 2-hourly or 25 mcg dissolved in 200 mL water, 25 mL given hourly	– Included in the WHO EML. – Make sure to use the correct dosage—overdose can lead to complications. – Do not use in women with previous cesarean section.
Cervical ripening prior to instrumentation (first trimester)	400 mcg vaginally 3 hours before procedure or 400 mcg sublingually 2–3 hours before procedure	– Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, and hysteroscopy.

Contraindications

- Hypersensitivity to misoprostol or to any of the excipients in the product
- Known allergy to prostaglandins

Contraindications in abortion setting

- Inherited porphyria
- Chronic or acute adrenal or hepatic failure
- Known or suspected ectopic pregnancy

Special warnings and precautions for use

Caution is warranted in women with preexisting heart disease or cardiovascular risk factors, as cardiovascular events have been reported in association with misoprostol.

Caution and clinical judgment are required for women using corticosteroids long term, and for those who have bleeding disorders or severe anemia.

When misopritol is used for induction of labor, the mother and her fetus should be closely monitored immediately after it is given.

When misoprostol is used for abortion, women should be advised to return for follow-up if they are experiencing signs of ongoing pregnancy.

Misoprostol should not be used in children below pubertal age.

This medicinal product contains hydrogenated castor oil. This may cause stomach upset and diarrhea.

Interaction with other medicinal products and other forms of interaction

Interaction studies show that the pharmacokinetics of propranolol and diazepam are not influenced by concomitant administration of misoprostol.

Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

In a pivotal study performed with misoprostol, no adverse events that would suggest the existence of an interaction between misoprostol and oxytocin were reported in women exposed to prophylactic oxytocin (intramuscular or intravenous) prior to administration of misoprostol.

Combination with nonsteroidal anti-inflammatory drugs

Theoretically, concomitant use with nonsteroidal anti-inflammatory drugs (NSAIDS) may reduce the efficacy of misoprostol. However, no clinically meaningful effect has been shown upon co-administration.

Pregnancy and lactation

Pregnancy

Misoprostol must not be used during intact pregnancy in the first trimester when the intent is to proceed, as a risk of fetal malformation cannot be excluded when misoprostol is administered during pregnancy.

In a few cases where misoprostol was self-administered (orally or vaginally) during early pregnancy, the following deleterious effects have been observed: malformations of limbs, abnormal fetus movements and cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Animal studies have not demonstrated teratogenicity but have shown fetotoxicity at high doses.

Available data regarding a potential risk of fetal abnormality after an unsuccessful medical abortion are limited and inconclusive; therefore, it is unnecessary to insist on termination of an exposed pregnancy if the woman wishes to continue it. Women should, nevertheless, be informed that due to the unknown risk to the fetus of abortifacient medicines, follow-up is important.

Breastfeeding

The levels of misoprostol in breast milk are low and decline very rapidly: after 5 hours of a single oral dose of 600 mcg, the levels in breast milk are unmeasurable and the risk to the infant is therefore minimal after a single dose. In practical terms, breast-feeding can be continued.

Fertility

Adverse effects on male or female fertility or reproduction were observed in rats at doses much higher than the maximum recommended human dose. Adverse effects on fertility or reproduction in humans seem unlikely.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Headache, dizziness, and tiredness have been reported during treatment with misoprostol. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are shivering and fever. In general, shivering and fever occur 60–90 minutes after misoprostol administration and are transient and short-lived.

List of adverse reactions

Safety of a misoprostol formulation has been evaluated in 1,428 women treated for PPH.

The adverse reactions reported in the clinical program are provided below and are classified according to frequency and system organ class. Undesirable effects are ranked under headings of frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency groupings are as follows:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000),
- Frequency not known (cannot be estimated from available data)

Adverse Reactions from Misoprostol

MedDRA	ADVERSE REACTIONS (FREQUENCY)			
SYSTEM ORGAN CLASS	VERY COMMON	COMMON	UNCOMMON	RARE
Nervous system disorders		Headache fainting/dizziness		
Gastrointestinal disorders	Nausea	Vomiting/diarrhea		
Skin and subcutaneous tissue disorders				Allergic reaction
General disorders and administration site disorders	Shivering fever, including temperature ≥40°C.	Chills	Fatigue	

When used for induction of labor, additionally uterine hyperstimulation and rupture as well as fetal distress may occur.

When used for abortion the following adverse events were reported in addition:

- Uterine cramping, prolonged menstrual-like bleeding, on average for 9 days (up to 45 days), incomplete abortion; rarely, genital tract infection and uterine rupture.

Women should be advised to return for follow-up if they experience prolonged heavy bleeding or fever.

Overdose

Symptoms linked to overdose of misoprostol are fever, blood pressure disorders, nausea, abdominal cramping, and tremors. There is no known antidote for misoprostol overdose. In the event of an overdose, the patient should be closely monitored.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of misoprostol products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on misoprostol tablets.

API

Misoprostol API is viscous oil, which must be stored below -20°C. It is extremely susceptible to degradation. Research established that a dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC) was considerably more stable than the pure misoprostol oil. Conventional tablets can be prepared from the solid misoprostol dispersion, with a shelf life of several years at room temperature.

As of February 2018, only one manufacturer of misoprostol dispersion (1:100 in HPMC) has been prequalified by the WHO PQP.

Manufacturer of WHO-Prequalified Misoprostol API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST PERIOD OR SHELF LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-226	Piramal Healthcare UK Ltd	Piramal Healthcare UK Ltd Whalton Road Morpeth Northumberland NE61 3YA, UK	Store in a refrigerator (2–8°C), protect from moisture and light.	60 months	4/22/2016

Two manufacturers of misoprostol API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturers of Misoprostol API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Misoprostol (monograph number 1731)	Chinoin Pharmaceutical and Chemical Works Private Co. Ltd, HU 1045 Budapest, Hungary	R0-CEP 2011-333-Rev 01	4/9/2014	Chemistry
Misoprostol (monograph number 1731)	Piramal Healthcare UK Ltd GB NE61 3YA Morpeth, UK	R1-CEP 2010-121-Rev 01	1/20/2017	Chemistry

Other manufacturers of misoprostol API should provide evidence for GMP compliance and API quality documentation as per the WHO guidelines.[1]

The specifications of misoprostol API should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP). The specifications of misoprostol dispersion should be in line with a pharmacopoeial monograph (Ph.Int. or USP).

Excipients

Excipients must conform to pharmacopeia monographs. The recommendations for the key excipients selection are listed below.

Filler: microcrystalline cellulose

Selection of the microcrystalline cellulose is likely to be important for tablet stability over the course of its shelf life. Because almost nine times the amount of microcrystalline cellulose is used compared to misoprostol 1% HPMC dispersion, the water content of this excipient will contribute most to the overall water content of the finished product.

Selected grades of Avicel® microcrystalline cellulose (FMC biopolymer) and their water content are shown below. Other manufacturers of microcrystalline cellulose make products with similar specifications.

Grades of Avicel® Microcrystalline Cellulose and Their Water Contents

PRODUCT GRADES	NOMINAL PARTICLE SIZE, µM	MOISTURE, %	LOOSE BULK DENSITY, G/mL
Avicel PH-102	100	3.0–5.0	0.28–0.33
Avicel PH-103	50	NMT 3.0	0.26–0.31
Avicel PH-113	50	NMT 2.0	0.27–0.34
Avicel PH-112	100	NMT 1.5	0.28–0.34

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

Two factors determine the selection of the grade of microcrystalline cellulose to use in the production:

1. Whether a drying stage is to be incorporated
    - If the microcrystalline cellulose will be dried to a low-moisture specification, then consider a microcrystalline cellulose with particle size compatible with dispersion for effective blending, and rheology of bulk and compression results (hardness, friability, low weight variation, etc.). The initial water content of the excipient will influence the drying time, but the rate of moisture absorption after drying should also be taken into account.
    - If no drying stage is incorporated, then a microcrystalline cellulose with the lowest moisture content, such as PH-112 (moisture not more than 1.5%), would seem appropriate to use.
2. Grade required for most efficient blending and tablet pressing
    - Selection of a grade which will result in more effective blending with the API may be critical to ensure content uniformity, rheology properties, and tablet pressing results. This is especially true for misoprostol 200 mcg tablets because the small amount of misoprostol API relative to the microcrystalline cellulose can make uniform blending challenging.

Disintegrant: sodium starch glycolate

This material is used to promote disintegration of the tablet and is recommended for use in tablets prepared by a dry compression process. Sodium starch glycolate is hygroscopic in nature. It swells rapidly when it comes in contact with water, resulting in rapid disintegration and dissolution. The European and US Pharmacopoeias differentiate the properties of sodium starch glycolate types A, B and C as summarized below.

Properties of Sodium Starch Glycolate

TEST	TYPE A	TYPE B	TYPE C
pH	5.5–7.5	3.0–5.0	5.5–7.5
NaCl	Max 7%	Max 7%	Max 1%
LOD	Max 10%	Max 10%	Max 7%
Assay Na	2.8–4.2%	2.0–3.4%	2.8–5.0%

Sodium starch glycolate type A with low moisture content should be used in the manufacture of misoprostol tablets.

Manufacturing process

Environmental conditions and moisture exclusion

Environmental conditions during all stages of the production, from weighing, blending, compression, and blistering should be carefully controlled to exclude moisture. Since misoprostol tablets are manufactured as a typical dry blend, much can be prepared in an 8-hour shift, from weighing of starting materials to cold aluminum formed blister packing.

Closed and continuous production systems are preferred to open and discontinuous processes.

The selection of the environmental temperature and relative humidity conditions may depend on the length of each of the stages of production, the time between stages, and how blended materials or bulk tablets are packed and stored.

If specific stages of production such as compression or blistering are expected to take more than several hours, consideration should be given to reducing the relative humidity for the stages to reduce overall exposure to moisture. Alternatively, storage of amounts of material needed for less than 1 hour of operations in sealed containers containing a desiccant should be considered. The use of desiccant should be studied carefully because in high–relative humidity conditions and/or prolonged storage it might create a microenvironment of high moisture and increase the risk of transfer of moisture to the bulk.

If desiccant is used to protect the bulk product, manufacturers should use airtight containers (aluminum, stainless steel, or other suitable canister) and replace the desiccant bags every time the canister is opened, or with frequency, to prevent moisture transfer. Desiccant bags should be dedicated and regenerated to prevent cross-contamination with other chemicals.

Good practice: suggested conditions for production are as follows:

- Temperature: not more than 25°C.
- Relative humidity: 30–50% depending on the length of time bulk blend or tablets are exposed to the atmosphere.
- Manufacturers should validate their production processes at the temperature and humidity levels selected for manufacture.

In-process controls

In a typical 200-mcg misoprostol tablet, 20 mg of the misoprostol 1% dispersion in HPMC is mixed with 180 mg of excipients. However, the actual content of misoprostol in the final product (200 mcg), is 0.1% the weight of a 200-mg tablet. The very low ratio of pure drug substance to the excipients can present a challenge to uniform blending, which will be critical to ensure good uniformity of content of finished product.

A validated blending process is critical, but sampling of the final blend from multiple locations in the bulk blend should be conducted for every batch to ensure the consistency of the blending process.

Hold times in production

Short holding times between stages of production reduce potential exposure to moisture. Validation of holding times longer than 8 hours should be studied with caution, because one of the critical factors is the acceptance criteria. The main objective of this manual is to reduce variability within a batch and among batches, and to aim for the most stringent limits to assure not only homogeneity within a batch and among batches but also to improve the shelf life of the finished product.

Good practice: All production processes from blending to blistering should be carried out in as short a time as possible to reduce the possibility of exposure to moisture during production.

Storage conditions during production

The best practice is to blend, tablet-press, and foil-pack misoprostol tablets in a single day's operation. Where this is not possible, amounts of material required for 1-hour operation should be packed in virgin bags with the best possible barrier to moisture. If thermo-sealing is not possible, plastic ties can be used. Double bagging is better than single bags and a sturdy secondary container (plastic or stainless steel drum) with tight sealing and light protection is preferred.

The inclusion of a desiccant for storage is recommended, but the use of desiccants between bags or inside the drums should be studied with care to avoid possible release of moisture from desiccant to bulk or tablets.

Packaging

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Packaging that reduces water vapor transmission should ensure stability of the medicine during its shelf life. At 38°C and 90% relative humidity, cold-form aluminum completely prevents water vapor transmission. PVC, by contrast, has much higher water vapor transmission rate (2.4–4 g/m^2/day) under these conditions, which may occasionally be experienced during storage in hot and humid countries. Different grades of PVC/PVDC are also more protective than PVC, but not as protective as aluminum. The table below shows water vapor transmission rates (WVTR) for selected packaging.

Comparative Moisture Barrier Properties of Blister Packaging Materials

	Typical WVTR G/M^2/DAY 38°C/90%RH
Cold-form aluminum	0.00
PVC/80g PVDC	0.31
PVG/60g PVDC	0.47–0.6
PVC/40g PVDC	0.7–0.75
PVC	2.4 –4.0

Good practice: Misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.

Suitability of the aluminum foil should be demonstrated, including:

- Safety: declarations as to compliance with appropriate food additive regulations (e.g., USFDA or EU regulations)
- Protection: WVTR and light transmission (LT) rate as per USP<671>
- Compatibility: accelerated and long-term stability data for the packaged finished products

Bioequivalence requirements

A randomized, single-blind, single-dose, two-treatment, two-period, crossover bioequivalence study in healthy adult female subjects under fasting conditions is required. An appropriate comparator product is Cytotec® (misoprostol 200 mcg tablet, Searle/Pfizer), purchased from an SRA market.

Misoprostol has a range of therapeutic indications, employing a variety of routes of administration. However, it should be noted that the bioequivalence between the proposed and comparator products demonstrated following oral administration cannot be extrapolated to the other routes of administration. To obtain the full range of indications and routes of administration for a misoprostol product, in addition to the bioequivalence study employing oral administration as described above, the following data are required:

- Data from a single-dose, crossover bioequivalence study employing sublingual administration. Proof of bioequivalence in this study would be considered sufficient information to grant indications employing sublingual and buccal routes of administration.
- Pharmacokinetic data (not necessarily a bioequivalence study) showing that, following vaginal administration, the proposed product produces in vivo misoprostol concentrations with a mean maximal concentration (Cmax) of at least 200 pg/mL (normalized for a 800-mcg dose) and an extent of absorption (area under the curve [AUC]) that exceeds that observed following oral administration of the product (on a dose-normalized basis).
- Further, additional dissolution data will be needed in order to accept the product for the indication of "induction of labor" due to the required administration of fractional doses.