Update on norms and standards for pharmaceuticals

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Norms and Standards for Pharmaceuticals

Role and Function:

- To develop & establish norms and standards for **pharmaceuticals**
- Promote their implementation and use of by WHO Member States, in collaboration with other WHO Teams, Regional and Country Offices

(Article 2, WHO Constitution)

Secretariat for the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)

First World Health Assembly (WHA1), Palais des Nations, Geneva, 24 June - 24 July 1948. Left to right: Dr Brock Chisholm, first Director-General of WHO, Dr Andrija Stampar, M. Henri Laugier, Assistant Secretary-General of the UN.

Specific areas of work

- Publish and maintain the International Pharmacopeia
- International Chemical Reference Substances (ICRS)
- Publish and maintain WHO recommendations for pharmaceuticals (QA compendium)
- Organize the External Quality Assurance Assessment Scheme (EQAAS)
- WHO Biowaiver Project

The International Pharmacopoeia, published by WHO, provides a valuable resource, especially to countries that do not have public standards to control the quality of products in their market.

Aligns with Global health policies

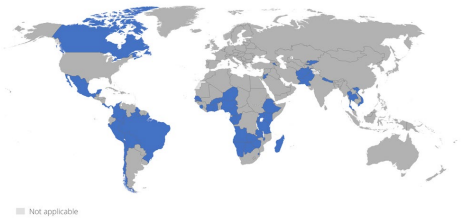
- WHO Model List of Essential Medicines
- WHO treatment guidelines
- Invitations to submit EOI for product evaluation to PQT-m

Use cases

- WHO Member States
- WHO Prequalification
- Response to COVID-19 and other emergencies

Outcomes

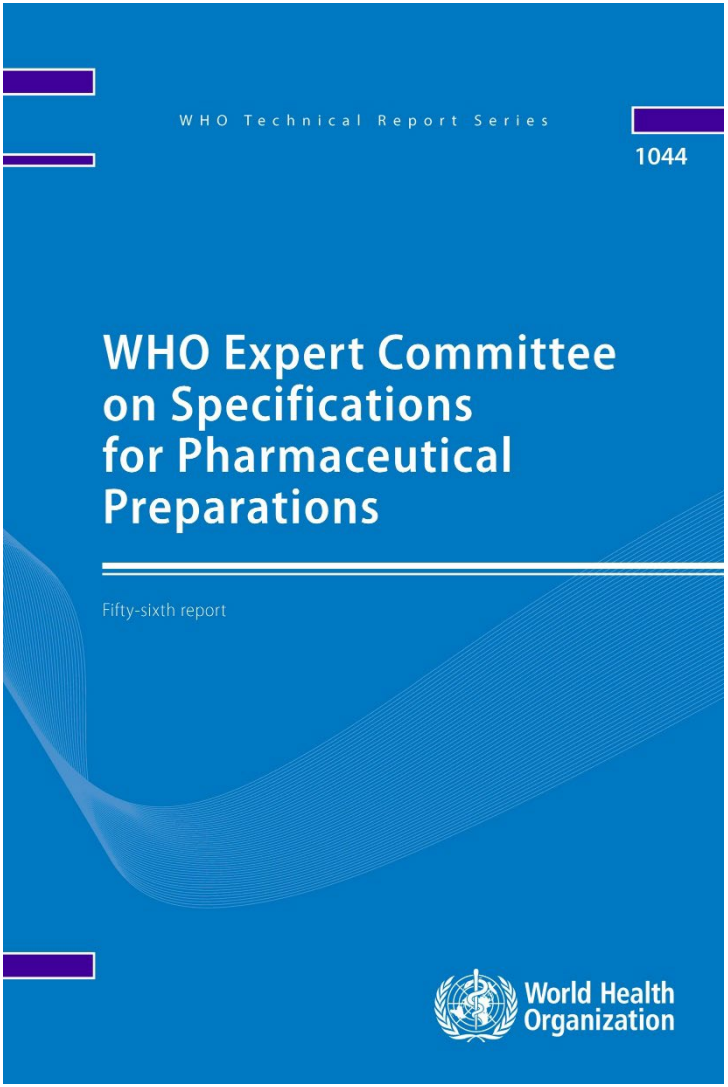
- Covers neglected diseases
- Specific dosage forms e.g., FDCs, child-friendly dosage forms
- Novel products, like COVID-19 therapeutics



More than 40 countries officially refer to the International Pharmacopoeia

WHO prequalification is used by UN agencies and all major global procurement agencies supplying to LMICs

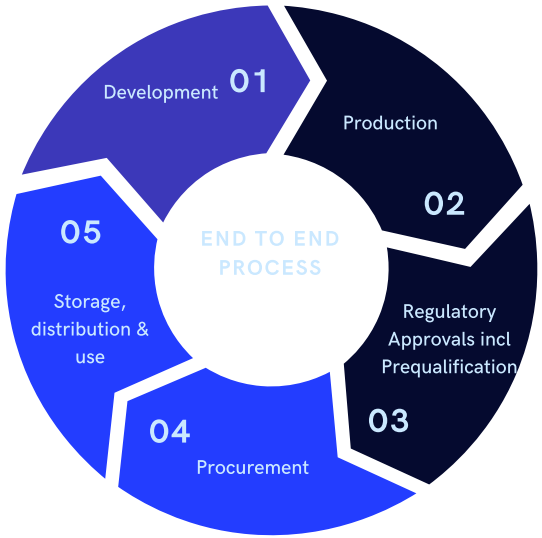
The International Pharmacopoeia 11th edition



WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)

Covers today **WHO's Norms and Standards for Pharmaceuticals*:***

- Quality control
- Regulatory standards
- Inspection



The 10th edition of WHO's Quality Assurance of Pharmaceuticals Compendium, Volume 2, is a crucial resource for safeguarding the quality, safety, and effectiveness of medicines.

Compendium empowers countries to establish robust regulatory systems and uphold international standards in pharmaceutical quality assurance.

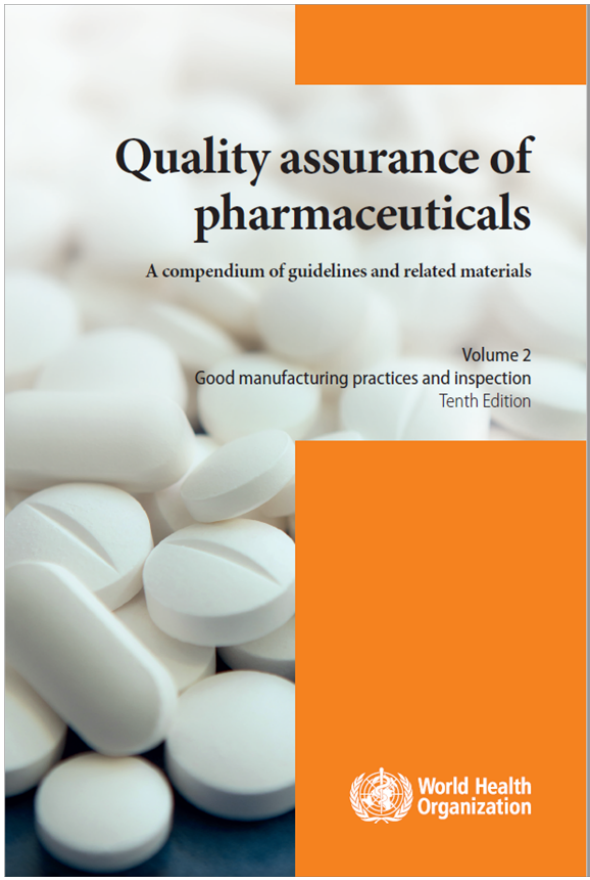
reflects the latest guidelines adopted by the Expert Committee on Specifications for Pharmaceutical Preparations (54th, 55th, 56th meetings).

forty-five guidelines

10 *revised guidelines*

8 *new guidelines*

Recommendations on environmental aspects for the prevention of antimicrobial resistance, health-based exposure limits in cleaning validation, and GXPs for R&D facilities



The WHO Biowaiver List classifies 34 products from the WHO EML since 2018 (TRS 1044, 2022)

MEDICINE[a]	THERAPEUTIC AREA	INDICATION	HIGHEST THERAPEUTIC DOSE (MG)	API PQ EOI/PQ	WHO CLASSIFICATION[b]
abacavir (sulfate)	**Antiretrovirals**	**Antiretrovirals (HIV)**	**600**	**Yes**	**I/III**
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV *
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	Yes	II/IV *
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	Yes	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
chloroquine phosphate	Antiprotozoals medicines	Antimalarial medicines	1000 mg salt (= 600 mg base)	No	I/III
codeine (phosphate hemihydrate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
cycloserine (hydrochloride)	Antibacterials	Antituberculosis medicines	1000	Yes	I/III
Daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV **
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV **
dexamethasone	(1) Gastrointestinal medicines (2) Immuno-modulators and antineoplastics (3) Medicines for pain and palliative care *(4) Corticosteroids for COVID-19[c]*	(1) Antiemetic medicines (2) Acute lymphoblastic leukaemia (2) Multiple myeloma (3) Medicines for other common symptoms in palliative care *(4) Treatment of patients with severe and critical COVID-19[c]*	(1) (3) 0.5 to 10 mg a day depending on the disease being treated (2) 40 mg *(4) 6 mg a day [c]*	Yes	I/III**
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV**
Doxycycline (hyclate)	**(1) Antiprotozoals (2) Antibacterials**	**(1)Antimalarial medicines (2)Antibiotics (access group)**	**100**	**No**	**I/III****
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
emtricitabine	Antiviral medicines	Antiretrovirals (HIV)	200	Yes	I/III**
entecavir	Antiviral medicines	Antihepatitis medicines	1	Yes	I/III**
Ethambutol (hydrochloride)	**Antibacterials**	**Antituberculosis medicines**	**2000**	**Yes**	**I/III**

MEDICINE[a]	THERAPEUTIC AREA	INDICATION	HIGHEST THERAPEUTIC DOSE (MG)	API PQ EOI/PQ	WHO CLASSIFICATION[b]
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV *
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
hydroxychloroquine (sulfate)	**Disease-modifying anti-rheumatic drugs (DMARDs)**	**Lupus erythematosus**	**600**	**No**	**I/III****
isoniazid	**Antibacterials**	**Antituberculosis medicines**	**300**	**Yes**	**I/III**
lamivudine	**Antiviral medicines**	**Antiretrovirals (HIV)**	**300**	**Yes**	**I/III**
levonorgestrel	**Medicines for reproductive health and perinatal care**	**Oral hormonal contraceptives**	**1.5**	**Yes**	**II/IV ***
mefloquine (hydrochloride)	Antiprotozoals medicines	Antimalarial medicines	1250 (as hydrochloride)	Yes	II/IV
methyldopa (sesquidrate)	Cardiovascular medicines	Pregnancy-induced hypertension	500	No	I/III
oseltamivir (phosphate)	Antiviral medicines	Influenza virus	75 (as phosphate)	Yes	I/III**
paracetamol	Medicines for pain and palliative care/ Antimigraine medicines	Non-opioids and non-steroidal anti-inflammatory medicines/ Treatment of acute attack	1000	No	I/III
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *P. vivax* and *P. ovale* infections)	15	Yes	I/III
Proguanil (hydrochloride)	**Antiprotozoal medicines**	**Antimalarial medicines**	**200**	**No**	**I/III**
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second-line)	400	Yes	II/IV**
rifampicin	Antibacterials	Antituberculosis/anti-leprosy medicines	750	Yes	II/IV
sofosbuvir	Antiviral medicines	Medicines for hepatitis C	400	Yes	II/IV**
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III**

Update on new guidelines and norms, and standards

Overview of the new guidelines, and monographs for pharmaceuticals discussed at the 57th ECSPP (9- 13 October 2023)

Guidelines discussed at the 57th ECSPP meeting – 9 – 13 October 2023

- **GMP related**
  - WHO good manufacturing practices for excipients used in pharmaceutical products (QAS/23.921/Rev1)
  - IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations (QAS/23.932/Rev1)
  - Good practices for pharmaceutical quality control laboratories (QAS/21.882)
  - WHO good manufacturing practices and inspection guidelines compendium: gap analysis for revisions/new text (QAS/23.931)
- **Medical devices**
  - WHO/UNFPA female condom generic specification (QAS/22.913/Rev2)
- **Regulatory topics**
  - WHO Biowaiver List
  - WHO guideline on Biopharmaceutics Classification System - based Biowaivers (QAS/23.929/Rev1
  - Guideline on bioanalytical method validation and study sample analysis (QAS/23.925)
  - WHO regulatory guidance and related texts: revisions/new texts for discussion (QAS/23.940)

Texts discussed: General Chapters & monographs

- Micro determination of water by the Karl Fischer method
- Melting temperature and melting range
- Chromatography
- Test for DEG and EG in liquid oral dosage forms
- Investigations to evaluate the suitability of the proposed procedures
- **Liquid preparations for oral use**

Texts discussed: Monographs

- **COVID-19 therapeutics**
  - Molnupiravir
  - Molnupiravir capsules
  - Nirmatrelvir
  - Nirmatrelvir tablets
- **Medicines for maternal, infant, child and adolescent health**
  - Estradiol valerate and norethisterone enantate injection
- **Medicines for tropical diseases**
  - Albendazole
  - Albendazole tablets
  - Albendazole chewable tablets

Texts discussed: Monographs

- **Antimalarial medicines**
  - Pyrimethamine tablets
- **Antituberculosis medicines**
  - Rifampicin
  - Test for MeNP in Rifampicin
- **Antiviral medicines, including antiretrovirals**
  - Efavirenz
  - Tenofovir disoproxil fumarate
  - Tenofovir disoproxil tablets
  - Lamivudine and tenofovir tablets
- **Other medicines**
  - Yttrium-(90Y)-silicate injection
  - Paracetamol oral solution

Updated WHO Biowaiver List

MEDICINE[a]	THERAPEUTIC AREA	INDICATION	HIGHEST THERAPEUTIC DOSE (MG)	API PQ EOI/PQ	WHO CLASSIFICATION[b]
amlodipine (besylate)	Cardiovascular medicines	Antihypertensive medicines	10	No	I/III
bisoprolol (fumarate)	Cardiovascular medicines	Antihypertensive medicines	20	No	I/III**
clindamycin (hydrochloride)	Antibacterials	Access group antibiotics	450	Yes	I/III
fluconazole (form III)	Antifungal medicines	Cryptococcosis and Candidosis	800	Yes	I/III
hydralazine (hydrochloride)	Cardiovascular medicines	Antihypertensive medicines (pregnancy-induced hypertension)	100	No	I/III
quinine (sulfate)	Antiprotozoal medicines	Antimalarial	648	No	II/IV*
ribavirin	Antiviral medicines	Viral haemorrhagic fevers	600	Yes	I/III**
valganciclovir	Antiviral medicines	Cytomegalovirus retinitis (CMVr)	900	Yes	I/III**

* Change in solubility class with respect to WHO 2006 classification.

**APIs characterized for the first time within the WHO Biowaiver Project.

The WHO List of International Comparator Products: A Key Resource to manufacturers and regulators for demonstrating interchangeability of generic medicines - New update Q4 2023!

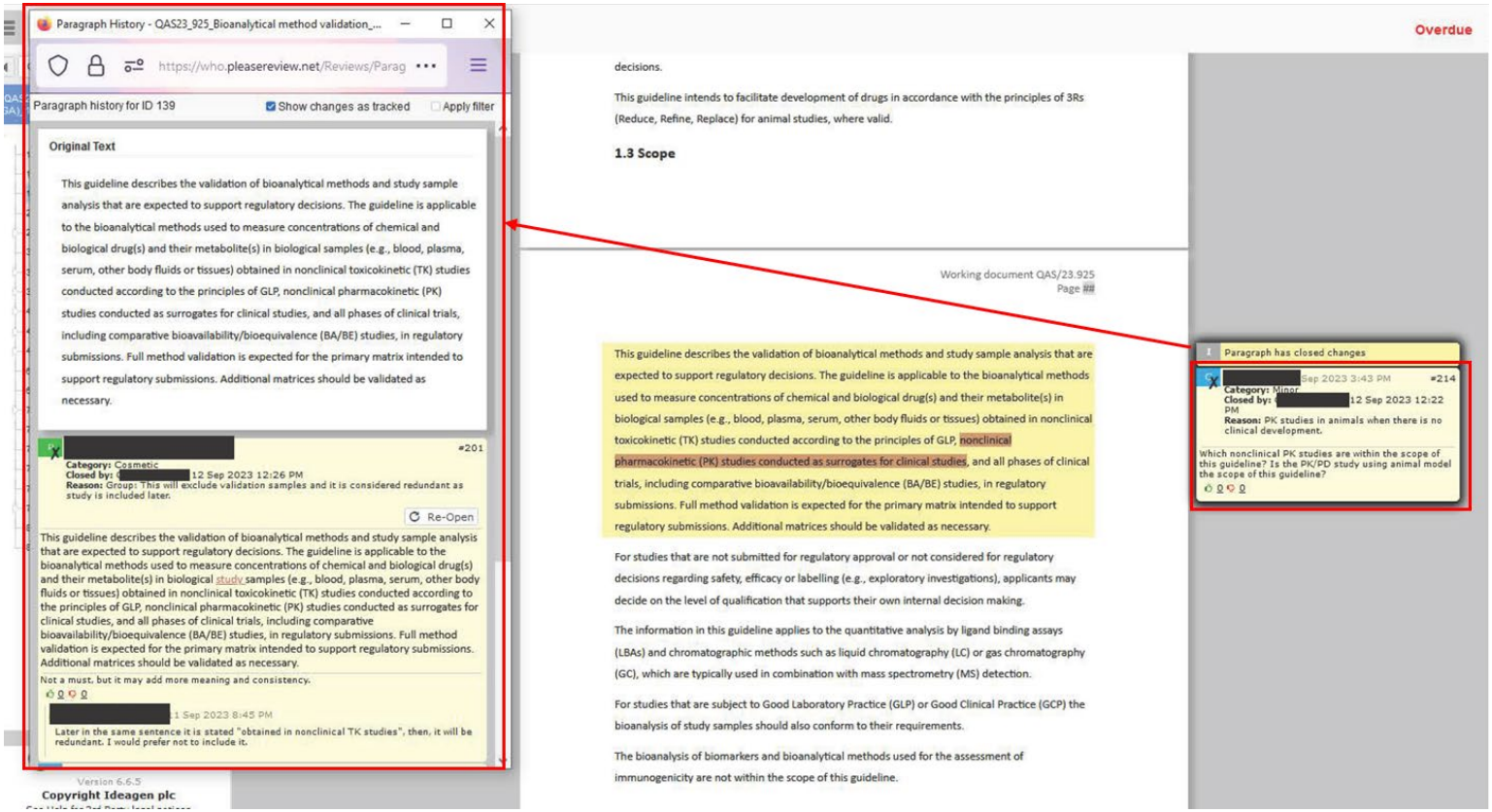
Essential Medicine Name	Essential Medicine List dosage form/ dose strengths	International comparator product	Marketing Authorisation Holder	Markets	PQ comparator product
abacavir (ABC)	Tablet: 300 mg (as sulfate).	Ziagen	ViiV Healthcare	SRA	Ziagen (300 mg tablet, GlaxoSmithKline)
abacavir (ABC)	Oral liquid: 100 mg (as sulfate)/5 ml.	Ziagen	ViiV Healthcare	SRA	Ziagen (20 mg/ml oral solution, GlaxoSmithKline)
acetazolamide	Tablet: 250 mg.	Diamox	Mercury Pharmaceuticals Ltd	EU	N/I
acetic acid	Topical: 2%, in alcohol.	Acetic acid (Solution, Otic drops)	Wockhardt	USA	N/I
acetylcysteine	Injection: 200 mg/ml in 10-ml ampoule.	Hidonac Antidoto 5 g/25 mL Fluimucil 200 mg/ml, solution for infusion Acetadote 6 g/30 mL	Zambon Zambon Cumberland Pharmaceuticals	EU EU USA	N/I
acetylcysteine	Oral liquid: 10%; 20%	Fluimucil or Flumil 20mg/mL	Zambon	EU	N/I
acetylsalicylic acid	Tablet: 100 mg to 500 mg.	Aspirin	Bayer	EU	N/I
acetylsalicylic acid	Suppository: 50 mg to 150 mg.	Resprin Suppositories 300 mg	Ricesteele Manufacturing Ltd.	United Kingdom	N/I
acetylsalicylic acid	Tablet: 300 mg to 500 mg.	Aspirin	Bayer	EU	N/I
acetylsalicylic acid	Tablet: 100 mg.	Aspirin	Bayer	EU	N/I
aciclovir	Ointment: 3% W/W.	Zovirax	GlaxoSmithKline / Wellcome	EU	N/I
aciclovir	Oral liquid: 200 mg/5 ml.	Zovirax	GlaxoSmithKline / Wellcome	EU	N/I
aciclovir	Powder for injection: 250 mg (as sodium salt) in vial.	Zovirax	GlaxoSmithKline / Wellcome	EU	Zovirax (GlaxoSmithKline)
aciclovir	Tablet: 200 mg.	Zovirax	GlaxoSmithKline / Wellcome	EU	Zovirax (GlaxoSmithKline)
albendazole	Tablet (chewable): 400 mg.	Eskazole	GlaxoSmithKline	EU	Eskazole 400 mg (chewable) tablet (GlaxoSmithKline) Albenza 200 mg (chewable) tablet (Amedra Pharms, USA)
allopurinol	Tablet: 100 mg.	Zyloric Zyloprim	Aspen or Faes Sebela Ireland LTD	EU USA	N/I
allopurinol	Tablet: 100 mg to 300 mg.	Zyloric Zyloprim	Aspen or Faes Sebela Ireland LTD	EU USA	N/I
amidotrizoate	Injection: 140 mg to 420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule.	Urografin	Bayer	EU	N/I

Guidelines Workplan – High Priority

WHO Guidance on GMP considerations for prevention and control of contamination of medicines with nitrosamines	New
Appendices to the GMP for Excipients used in Pharmaceutical Products: I)Points to consider document focusing on a risk management-based approach for excipients with possible impurities; II)List of high-risk excipients (e.g. considering contamination with diethylene glycol-DEG, ethylene glycol-EG, nitrosamines).	New
Good practices on market surveillance and control	New
Guidelines on packaging for pharmaceutical products (Annex 9, TRS 2012, 2002)	Revision
WHO guidelines for sampling of pharmaceutical products and related materials (Annex 4, TRS 929, 2005)	Revision
Development of paediatric medicines: points to consider in formulation (Annex 5, TRS 970, 2012)	Revision

WHO general guidance on variations to multisource pharmaceutical products (Annex 10, TRS 996, 2016)	Revision
WHO good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions	Revision
WHO good manufacturing practices for pharmaceutical products: Main principles	Revision
Guidelines for registration of fixed-dose combination medicinal products (Annex 5, TRS 929, 2005)	Revision
Points to consider on the implementation of e-labelling (e-leaflet or e-PIL)	New
Guidelines for safe disposal of unwanted pharmaceuticals	New
Guideline on Regulatory Information Management System (RIMS)	New

Introduced online system (PleaseReview®) to facilitate the drafting and feedback from experts and during public consultation



Thank you

www.who.int/teams/health-product-policy-and-standards/overview

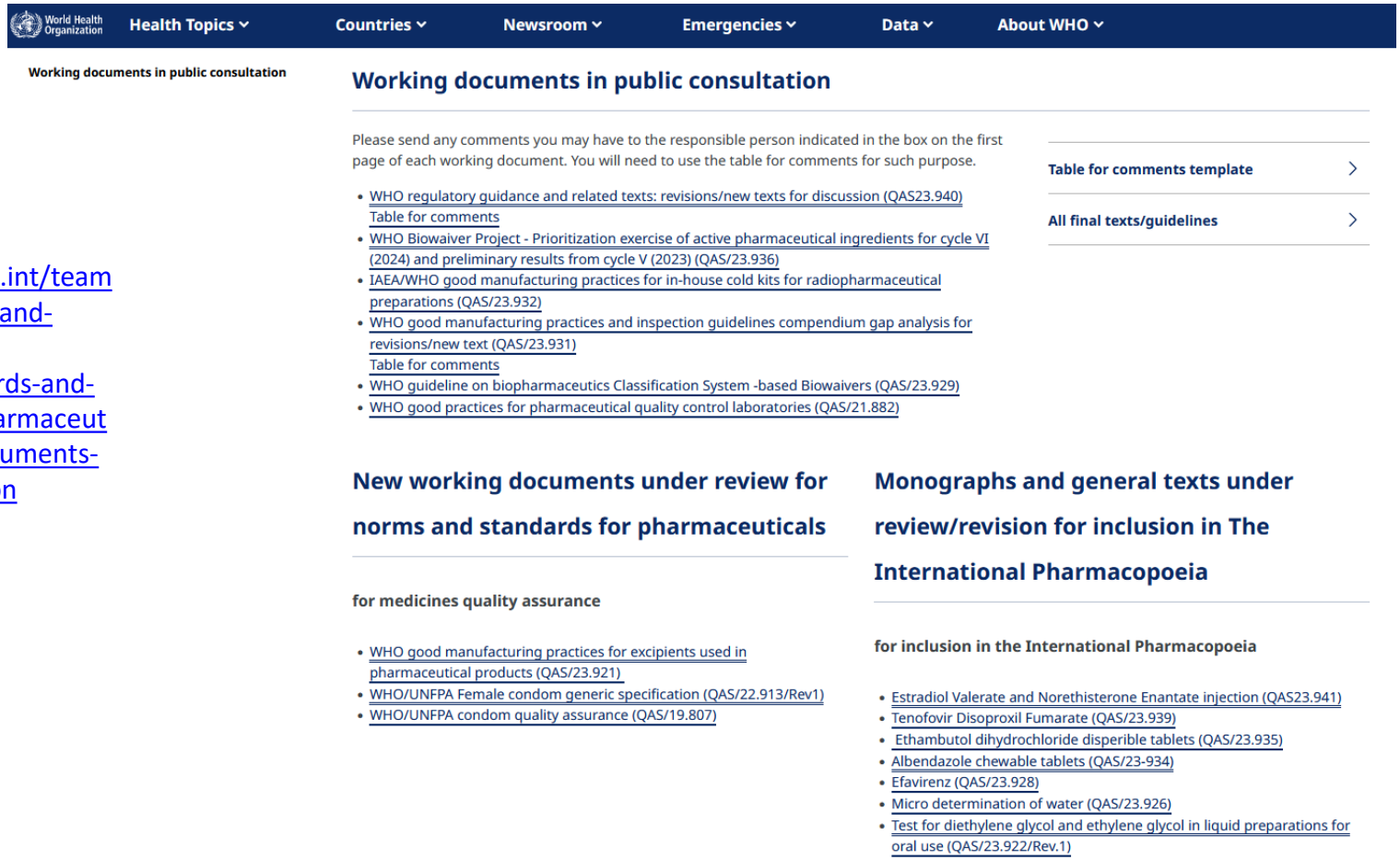
Back-up slides

WHO Biowaiver Project: Cycle VI

N	API contained in medicines on the EML	Therapeutic Area	Highest therapeutic single dose
1	Amitriptyline (hydrochloride)[a]	Medicines for mental and behavioural disorders	75 mg
2	Biperiden (hydrochloride)[a]	Anticholinergic medicines	2 mg
3	Cefalexin (monohydrate)	Antibacterials	2000 mg
4	Hydrochlorothiazide[a]	Cardiovascular medicines	100 mg
5	Linezolid (repetition of cycle V experiments)	Antibacterials	600 mg
6	Miltefosine	Antiprotozoal medicines	50 mg
7	Misoprostol	Uterotonic medicines	800 µg
8	Pyrazinamide[a]	Antibacterials	2000 mg
9	Zidovudine[a]	Anti-infective medicines	300 mg

Where can you find “Current projects“?

https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation



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Working documents in public consultation

Working documents in public consultation

Please send any comments you may have to the responsible person indicated in the box on the first page of each working document. You will need to use the table for comments for such purpose.

- WHO regulatory guidance and related texts: revisions/new texts for discussion (QAS23.940)
  Table for comments
- WHO Biowaiver Project - Prioritization exercise of active pharmaceutical ingredients for cycle VI (2024) and preliminary results from cycle V (2023) (QAS/23.936)
- IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations (QAS/23.932)
- WHO good manufacturing practices and inspection guidelines compendium gap analysis for revisions/new text (QAS/23.931)
  Table for comments
- WHO guideline on biopharmaceutics Classification System -based Biowaivers (QAS/23.929)
- WHO good practices for pharmaceutical quality control laboratories (QAS/21.882)

Table for comments template

All final texts/guidelines

New working documents under review for norms and standards for pharmaceuticals

for medicines quality assurance

- WHO good manufacturing practices for excipients used in pharmaceutical products (QAS/23.921)
- WHO/UNFPA Female condom generic specification (QAS/22.913/Rev1)
- WHO/UNFPA condom quality assurance (QAS/19.807)

Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia

for inclusion in the International Pharmacopoeia

- Estradiol Valerate and Norethisterone Enantate injection (QAS23.941)
- Tenofovir Disoproxil Fumarate (QAS/23.939)
- Ethambutol dihydrochloride disperible tablets (QAS/23.935)
- Albendazole chewable tablets (QAS/23-934)
- Efavirenz (QAS/23.928)
- Micro determination of water (QAS/23.926)
- Test for diethylene glycol and ethylene glycol in liquid preparations for oral use (QAS/23.922/Rev.1)