Update on
WHO Public Assessment Reports

Regine Lehnert, MD

Outline

- **The WHO Public Assessment Reports (WHOPARs)**
  - **Why** they are prepared
  - **Where** to find them
  - **What** they contain
  - **How** they are prepared
  - **Who** prepares them

- **The product information in the WHOPAR ➡ (SmPC / PIL)**
- **Updates**

WHOPARs – Why

World Health Assembly Resolution WHA57.14 (2004)

WHO Public Assessment Reports (WHOPARs)
are a **key output** of the WHO Prequalification Team/Medicines, providing **insight and transparency as to the process** followed to prequalify the finished pharmaceutical products (FPPs) concerned.

A WHOPAR is of great value **for regulators and procurers**. As well as **summarizing the assessment** of the data and information provided by the manufacturer, it describes the **quality, safety and efficacy** of the prequalified product. (… .)

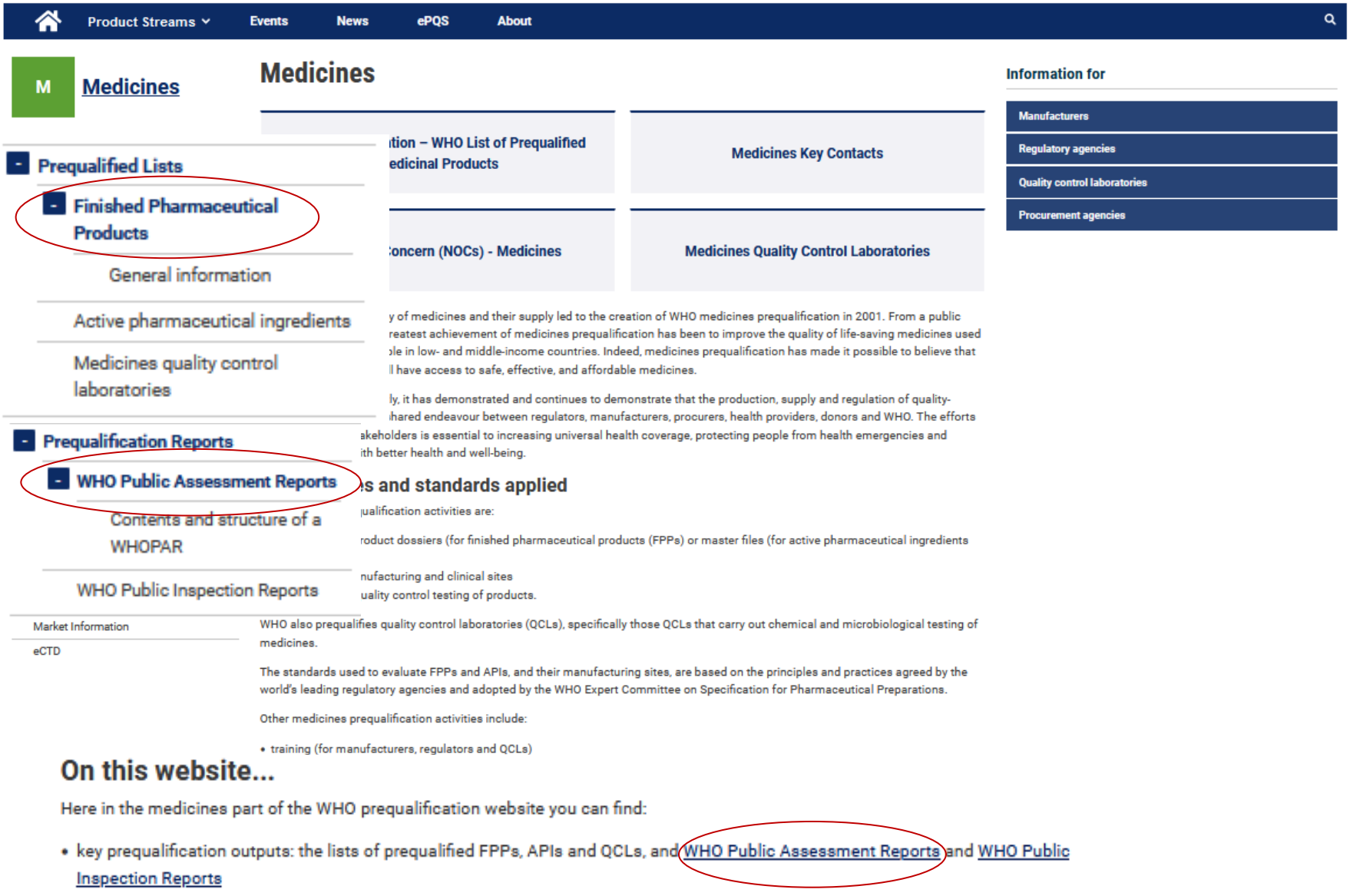
https://extranet.who.int/prequal/medicines

WHOPARs – Where to find them

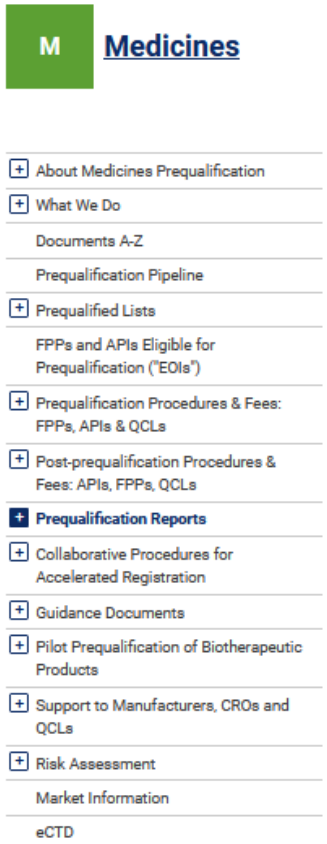
Do not Google them! It may take you to outdated versions!

https://extranet.who.int/prequal/medicines

WHOPARs – Where to find them



WHOPARs – Where to find them



WHO Public Assessment Reports (WHOPARs) Medicines

Each WHO Public Assessment Report is listed by WHO reference number and therapeutic area. Each listing also provides the relevant International Nonproprietary Name (INN), the dosage formulation and dosage strength, and the name of the supplier.

The summary of product characteristics/patient information leaflet included in these WHOPARs focus on uses of the medicines covered by WHO Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised). The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

Refer to the **Contents and structure of a WHOPAR** section for information about the value of WHOPARS and the information they contain.

Therapeutic Area

COVID-19 Apply

M **BT-CV001**
Tocilizumab 20mg/mL (Each vial contains 80mg of tocilizumab in 4mL) - Concentrate for solution for infusion Roche Registration GmbH Germany

M **BT-CV002**
Tocilizumab 20mg/mL (Each vial contains 200mg of tocilizumab in 10mL) - Concentrate for solution for infusion Roche Registration GmbH Germany

M **BT-CV003**
Tocilizumab 20mg/ml (Each vial contains 400mg of tocilizumab in 20mL) - Concentrate for solution for infusion Roche Registration GmbH Germany

M **CV004**
Dexamethasone (sodium phosphate) 4mg/ml - Solution for injection Farmak JSC Ukraine

M **CV005**
Dexamethasone (sodium phosphate) 3.3mg/ml (1ml) - Solution for injection Noridem Enterprises Ltd Cyprus

WHOPARs- Where to find them

Overview of WHO Public Assessment Report (WHOPAR)

CV004

WHOPAR

Part 1	Part 2	Part 3	Part 4
Part 5	Part 6	Part 7	Part 8

M

Product name
Dexamethasone (sodium phosphate)

Dosage
4mg/ml - Solution for injection

Laboratory
Farmak JSC
Ukraine
Part 1 - Abstract
Part 2 - All accepted presentations (including photo)

** This summary of product characteristics/patient information leaflet focus on uses of the medicine covered by WHO Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).*
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

WHOPARs – How prepared

(focus on product information)

Step 1	• Submission of Product information with application for PQ
2	• Evaluation of quality and crosslinking attributes by PQ assessment team
3	• With positive assessment and inspection outcome compilation of the WHOPAR
4	• Forwarding to applicant for review (soft copies)
5	• Critical review by applicant, including annotations, where required substantiated by relevant data
6	• Return to WHO (soft copy) – if compressed, only as Zip folder
7	• If acceptable, publication. Otherwise repeat from step 4

WHOPARs –Who prepares them

WHOPAR-Group at PQT/MED

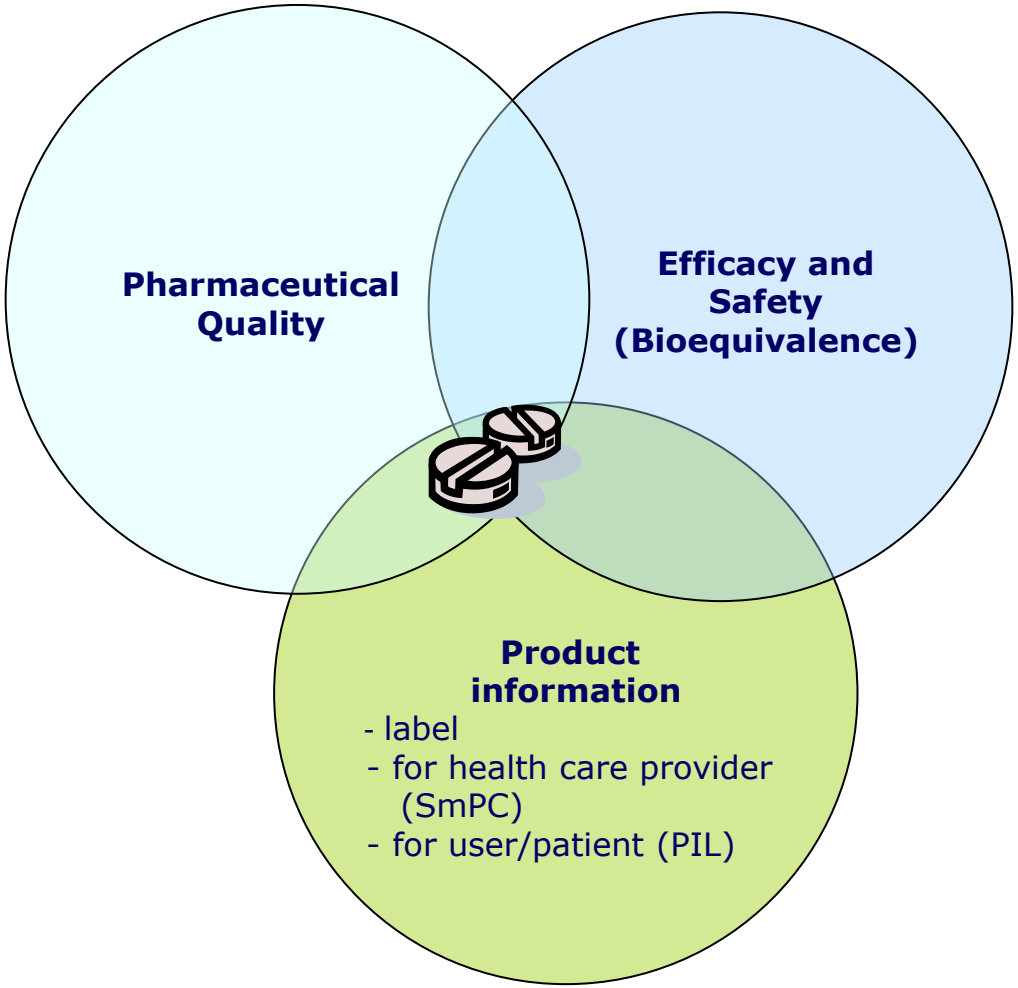
International group of experts
mainly from regulatory authorities
providing output on

- Prequalification processes and outcomes
- Information on efficacy and safety of prequalified products
- Focus on product information

→ Patient safety

- Parts 3 and 4: Based primarily on comparator product's information and WHO Treatment Guidelines

A Medicinal Product



WHOPAR Product information
clinical and preclinical sections

With time

- Revision of WHO treatment guidelines
- Update of reference product's information
- Availability of novel medical products
- Emergence of new scientific data

→ Information gets outdated

→ Same type of product WHOPARs with differing information

→ Products are prequalified that are not recommended by WHO anymore

WHOPAR-Product Information

WHO-PQ recommended

(generic) texts of clinical and preclinical medicines information

- In a rolling system
  (one product type/kind at a time,
  e.g. all abacavir-containing products)
- Regular updates begun in 2019:
  - **immediately** for major safety updates
    otherwise, **updates as needed**

Of note: This service provided by WHO does not in any way preclude the supplier's responsibility and liability in terms of keeping the product information of the supplied medicinal product correct and updated.

WHOPAR-Product Information

Periodic updates

- **First updates of most prequalified products**
  of all WHOPAR-parts for formatting updated and including, e.g. also requalification status
  60 "batches", **in 2024,** e.g. hepatitis antivirals, various reproductive health medicines, medicines for NTDs

- **Second periodic updates** of **15 "batches"**, more than **140 WHOPARs**

- **Safety updates** for AQ+S/P containing products

Status 12/2024

WHOPARs not updated

WHO Prequalification Programme
WHO PUBLIC ASSESSMENT REPORT (WHOPAR)

[trade name][1]

Kanamycin (as sulfate) 500mg/2ml Solution for Injection [1]

Abstract

[trade name], manufactured [redacted], was included in the WHO list of prequalified medicinal products for the treatment of tuberculosis on 06 February 2019.

[trade name], is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by kanamycin-sensitive strains of *Mycobacterium tuberculosis*. Kanamycin is only indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance.

Detailed information on the use of this product is described in the summary of product characteristics (SmPC), which can be found in this WHOPAR.

The active pharmaceutical ingredient (API) of [TB327 trade name], is the antimycobacterial agent kanamycin. The API is well established and documented for the treatment of tuberculosis.

The most serious safety concerns with kanamycin are nephrotoxicity and ototoxicity.

Other adverse reactions reported are anaphylaxis, hypersensitivity reactions, rash, anaemia, blood dyscrasias, purpura, headache, nausea, vomiting, diarrhoea, stomatitis, antibiotic-associated colitis, electrolyte disturbances, and effects on liver function. The "malabsorption syndrome" characterized by an increase in faecal fat, decrease in serum carotene, and fall in xylose absorption, has occurred with prolonged therapy.

Local reactions have included pain at the injection site after intramuscular injection.

The efficacy and safety profile of kanamycin is well established based on extensive clinical experience in the treatment of tuberculosis.

On the basis of data submitted and public information on the use of kanamycin in antituberculosis therapy, the team of assessors advised that [trade name], is of acceptable quality, efficacy and safety to allow inclusion of [TB327 trade name], in the list of prequalified medicinal products.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Summary of Prequalification Status for [trade name].

Initial acceptance	Date	Outcome
Status on PQ list, i.e. date of listing	[redacted]	listed
Quality	[redacted]	MR
Bioequivalence	[redacted]	MR
Safety, Efficacy	NA [redacted]	NA
GMP (re-)inspection		
API	[redacted]	MR
FPP	[redacted]	MR
GCP/GLP (re-)inspection	NA	NA

MR: meets requirements
NA: not applicable, not available

Clinical information not updated - no longer recommended for prequalified indication

Watermarks in parts 1, 3 and 4

Plain language descriptions of oral dosage forms

The description of visual appearance of finished product and packaging provided in the WHOPAR is important.

It can help the patient and health care provider

- To know that the information relates to the correct medicine (for example if a patient has multiple medicines, each with a patient information leaflet)
- to see if there is an obvious problem with the medicine (e.g. tablets are mottled when they are described as plain)
- to identify cases of falsification or error (if the description and the actual medicine do not match)

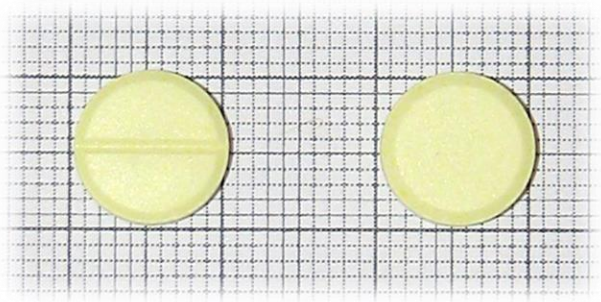
Descriptions of oral dosage forms – Issues noted

- Products with similar appearances may be described differently by different suppliers, and it may not be clear exactly what details are helpful to include
- Where technical language is used to describe aspects of the appearance it is likely to be confusing to readers unfamiliar with the terms
- The description is often a single complex sentence that can be hard to read

Case Study 1

- Yellow-coloured, circular, uncoated, flat-faced, bevelled edged, matt finished tablets, with a break line on one side and plain on the other side.
- A yellow, round, flat-faced, beveled edge tablet with a break line on one side and plain on the other side
- Yellow, circular, uncoated, matt-finished tablets. They are flat-faced and bevel-edged. The tablets have a break line on one side and are plain on other side.

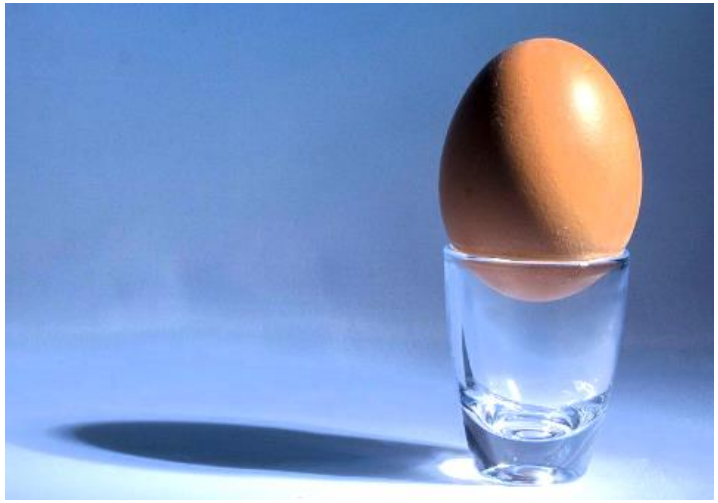
- Yellow, round, uncoated tablets. They are flat on the top and bottom with a bevelled edge. The tablets are plain on one side and have a score line on the other side.



Case Study 2

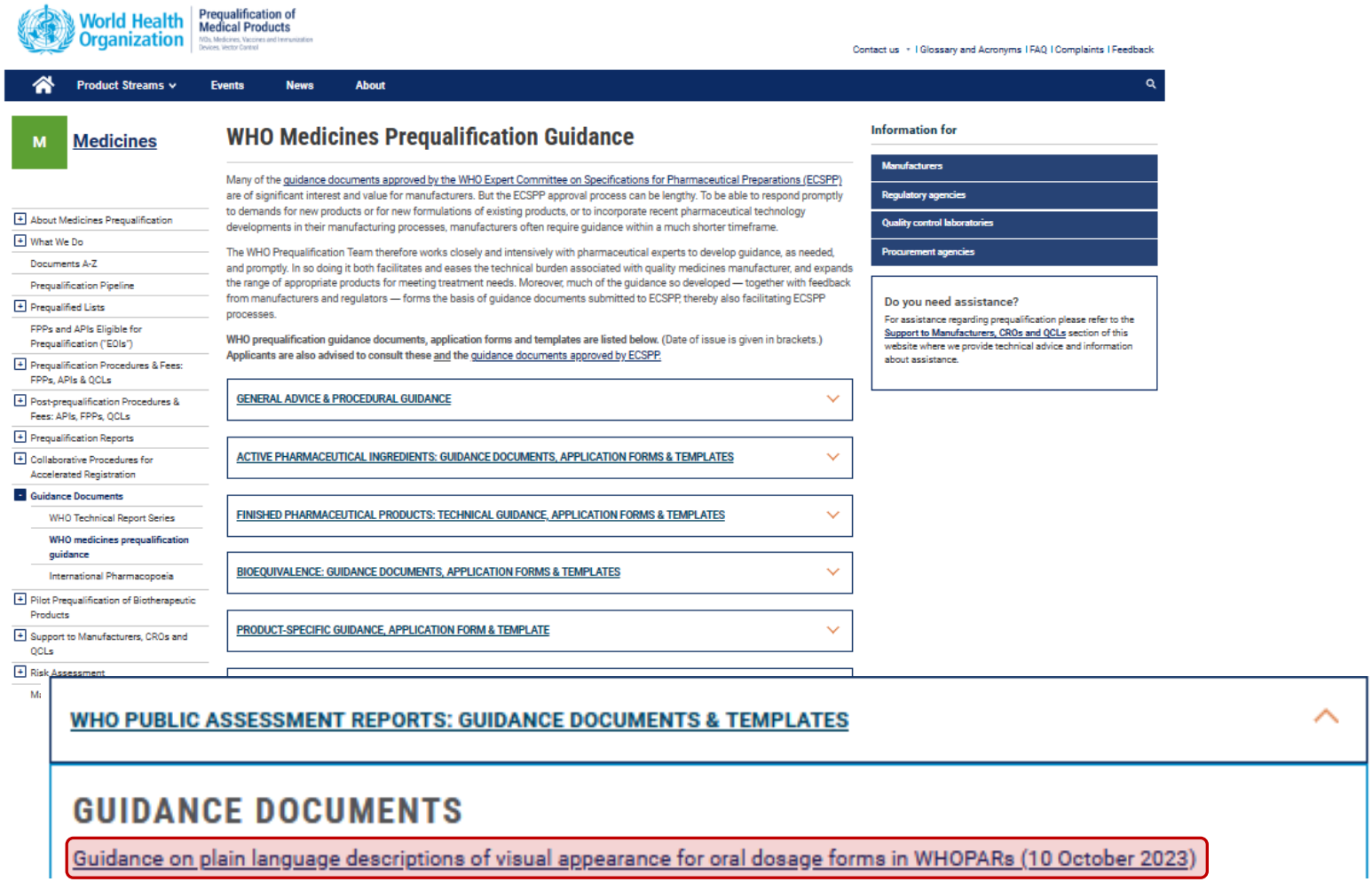
- Hard ovoid calcium carbonate capsule, buff to coffee-coloured, containing gallinaceous DNA in a spherical jasmine to gamboge-coloured lipoprotein delivery system suspended in a clear, viscous albuminaceous support solution.

- Brown egg



→ Similar issue for description of packaging

Plain language descriptions of oral dosage forms - WHO guidance



Mobile Technologies – QR*code in product information

Pros	Cons

*Quick Response

Mobile Technologies – QR code in product information

- PQT/MED supports the use of mobile technologies where appropriate, provided that
  - ✓ unrestricted access to this information for users, dispensers and prescribers is ensured and
  - ✓ local regulations in each target country are considered
- Decision on acceptance of mobile technologies is with National Regulatory Authorities (NRAs)
- Review of the printed and digital product information rests with the NRAs

Special excipients – in the WHOPARs

PQT/MED refers to EMA-Excipients Guideline: https://www.ema.europa.eu/en/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human

Two exceptions

- Lactose
- Sodium

General statement

If any excipient warnings are included, the WHOPAR product information states:

"It is important to consider the contribution of excipients from all the medicines that the patient is taking."

Non-functional or interchangeable excipients, e.g. colourants

Use of these excipients in medicinal products may lead to:

- A restriction in the target population
- Consequences on drug safety

→ **This aspect is now being highlighted in WHOPAR part 1.**

- **Avoiding such excipients with recognised undesirable action or effect in certain circumstances might confer advantage**

Example for Part 1 excipient statement

WHO Prequalification Programme

WHO PUBLIC ASSESSMENT REPORT (WHOPAR)

[RefNo trade name][1]

API tablets

[RefNo trade name], manufactured at […] was included in the WHO list of prequalified medicinal products for neglected tropical diseases on ss month yyyy.

[RefNo trade name] is indicated for treatment of […]. Detailed information on the use of this product is described in the summary of product characteristics (SmPC), which can be found in this WHOPAR.

{RefNo trade name} {DotWP-ProductName} contains <an excipient which restricts> <excipients which restrict> its use <in affected group (e.g. children)>; see WHOPAR part 3 (section 2) and part 4 (section 4.4) for more information.

The active pharmaceutical ingredients of [RfeNo trade name] is API.

[…]

Update on „SRA-WHOPARs“

Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

(trs986-annex5.pdf)

“WHO may request additional data, when considered necessary for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information, relevant for use of the product within the scope of the Prequalification Programme, will be included in the WHO public assessment report (WHOPAR) as a separate piece of information. Such information could be communicated to the reference SRA where appropriate. **The SRA-approved product information will not be changed**. “

News on „SRA-WHOPARs“

However

SRA-approved product information often not reflective of WHO-recommended uses

- Therapeutic indications, e.g. complicated bacterial infections versus DR-TB
- Target populations
- Dosing regimens
- Use in pregnancy and breastfeeding

News on „SRA-WHOPARs“

Note with respect to WHO PQT/MED Recommended Product Information additional to the SRA Approved Product Information for Products Prequalified via the Abridged (SRA) Route (29 March 2023)*

“Additional information, relevant for use of the product within the scope of the Prequalification Programme … in the WHO public assessment report (WHOPAR) as a separate piece of information”.

In accordance with this provision, for products prequalified based on SRA approval, hyperlinks to “WHO-PQ recommended patient information leaflet” and “WHO-PQ recommended summary of product characteristics”, which are generic for the respective kind of product, e.g. dolutegravir 50mg tablets, as applicable, will be published with the WHOPAR.”

*http://extranet.who.int/prequal/key-resources/documents/note-respect-who-pqtmed-recommended-product-information-additional-sra


Thank you
Tak
Dziękuję
Ευχαριστώ
Kiitos
Hvala
Obrigado
謝謝
Merci
Danke
Terim
Tack
תודה
Gracias
Thank you
Grazie
شكرا
謝謝
감사합니다
ありがとう
Спасибо
Спасибі