# 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

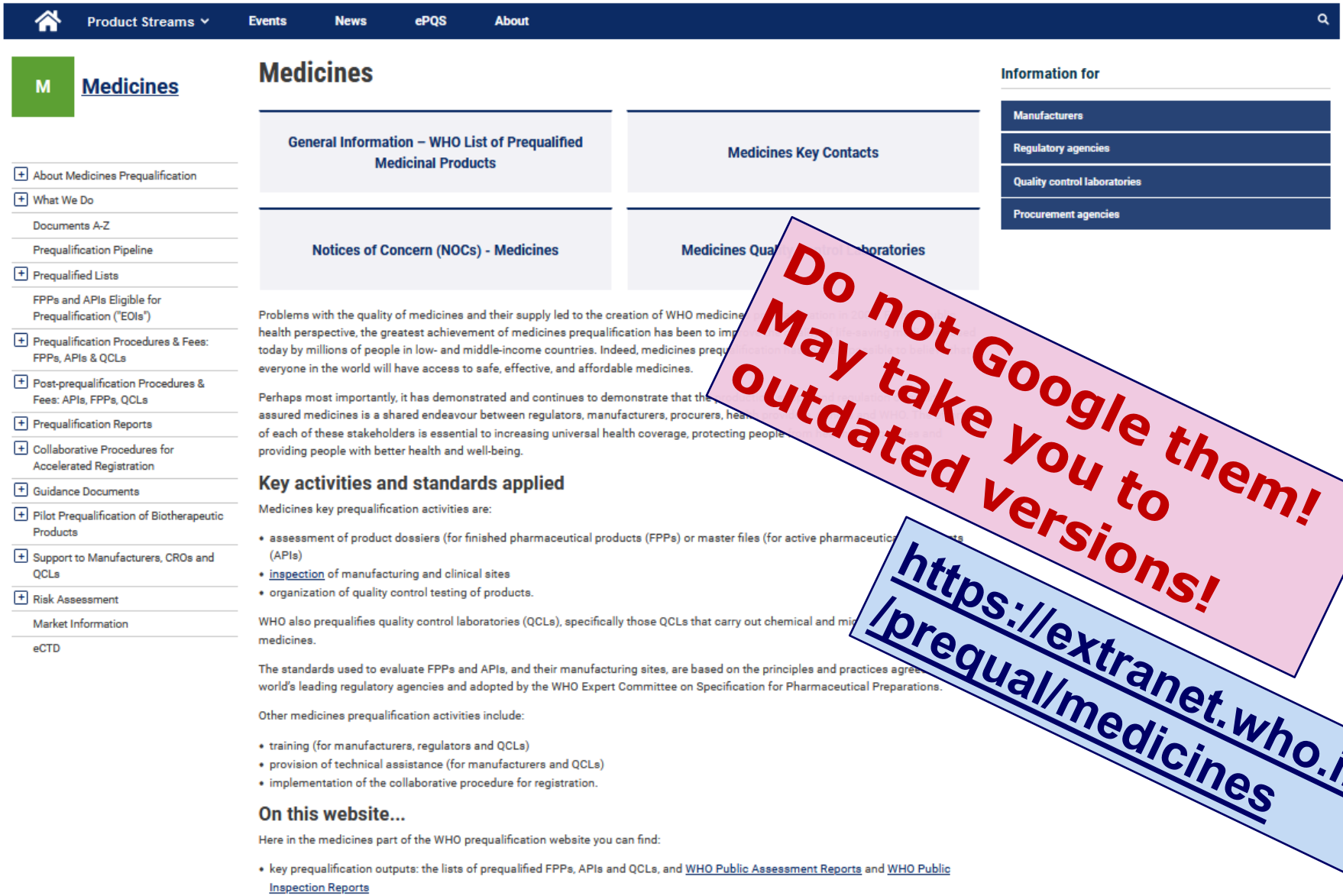
WHO Public Assessment Reports (WHOPARs) are a **key output** of the WHO Prequalification Team/Medicines, providing **insight and transparency as to the process** followed to prequalify the finished pharmaceutical products (FPPs) concerned.

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. (… .)

**World Health Assembly Resolution WHA57.14 (2004)**
***„To ensure that the prequalification review process and the results of inspection and assessment of the listed products, aside from proprietary and confidential information, are publicly available.“***

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

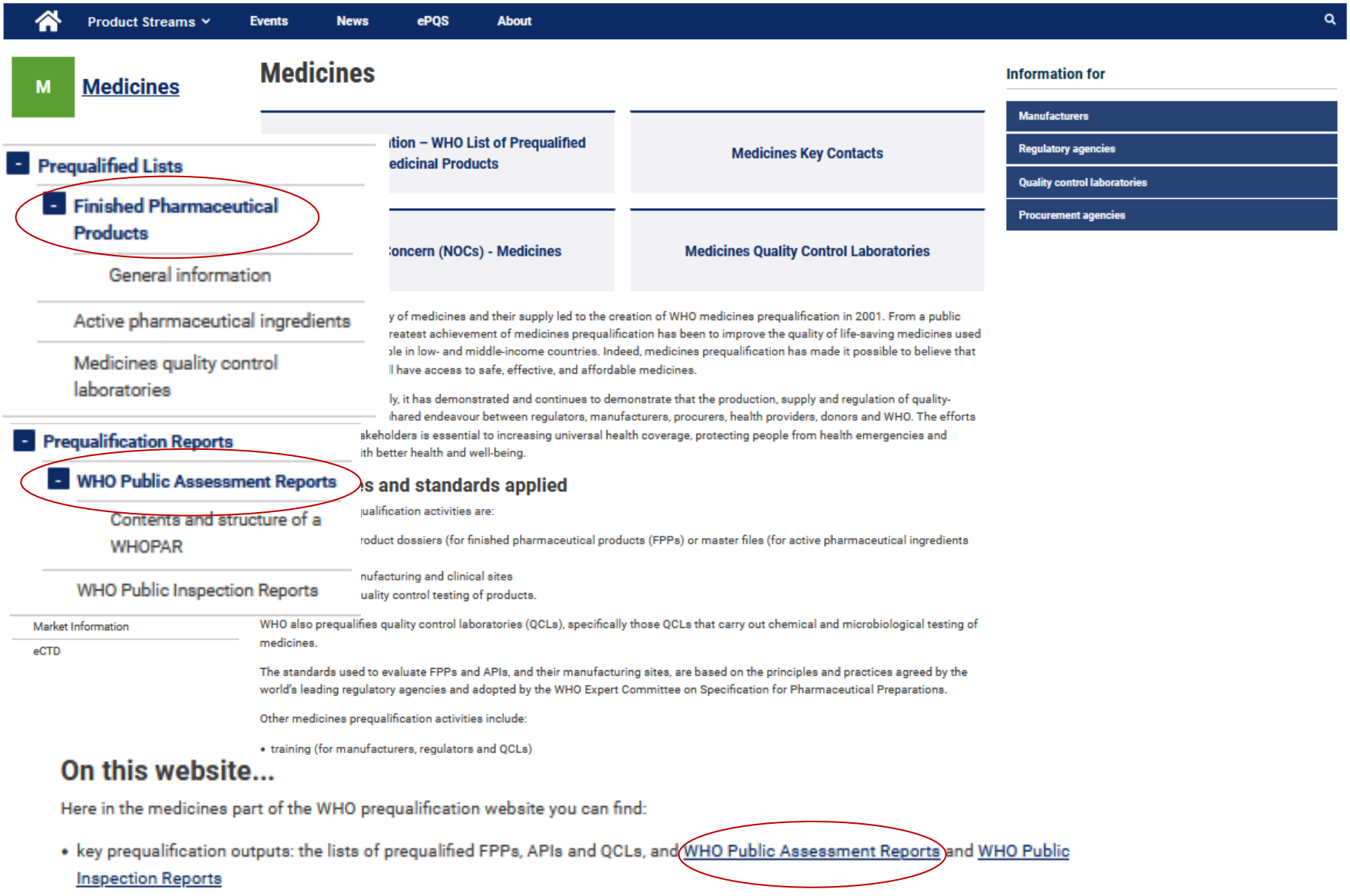
# WHOPARs – Where to find them




**Do not Google them!**
**May take you to outdated versions!**

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

# WHOPARs – Where to find them



# WHOPARs – Where to find them

M Medicines

- About Medicines Prequalification
- What We Do
- Documents A-Z
- Prequalification Pipeline
- Prequalified Lists
- FPPs and APIs Eligible for Prequalification ("EOIs")
- Prequalification Procedures & Fees: FPPs, APIs & QCLs
- Post-prequalification Procedures & Fees: APIs, FPPs, QCLs
- **Prequalification Reports**
- Collaborative Procedures for Accelerated Registration
- Guidance Documents
- Pilot Prequalification of Biotherapeutic Products
- Support to Manufacturers, CROs and QCLs
- Risk Assessment
- Market Information
- eCTD

## 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 PQTm

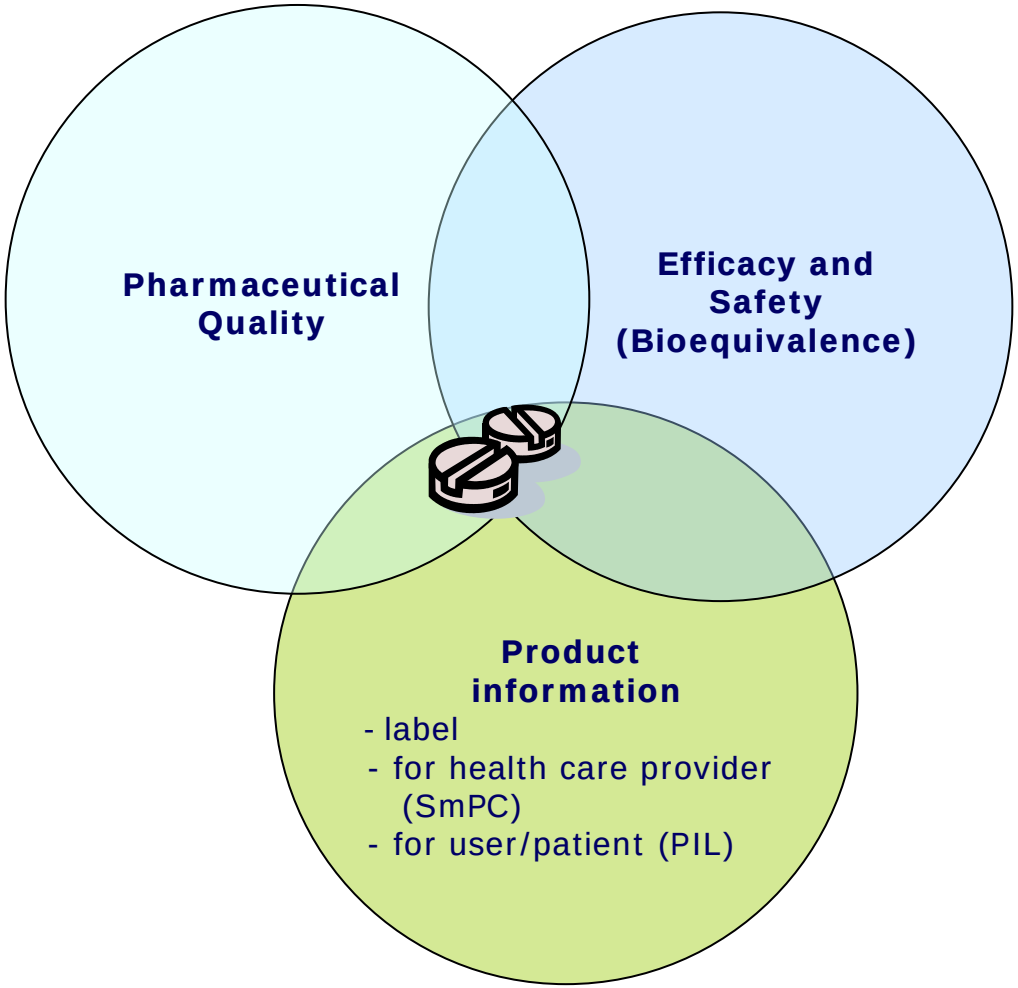
International group of experts
mainly from regulatory authorities
providing output on

- 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 “Good” 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 more than 260 WHOPARs**
  of all WHOPAR-parts for formatting updated and including, e.g. also requalification status
  **41 "batches"**, e.g. A/L, Dolutegravir, Moxifloxacin- many FDCs

- **Second periodic updates** of more than **60 WHOPARs**

- **Safety updates** for efavirenz- and dolutegravir-containing products

**Status 11/2023**

# 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

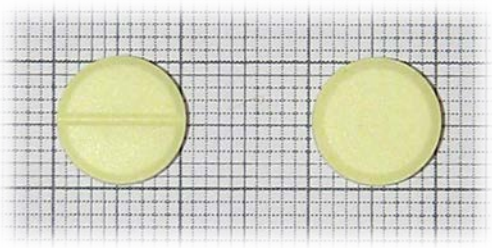
- To know that the information relates to the correct medicine (for example if a patient has multiple medicines, each with a patient information leaflet)
- to see if there is an obvious problem with the medicine (e.g. tablets are mottled when they are described as plain)
- to identify cases of falsification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

# Plain language descriptions of oral dosage forms

- 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

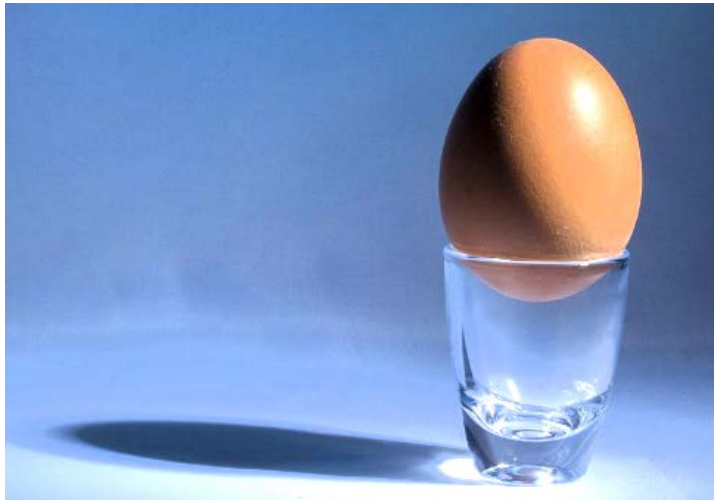
- Yellow-coloured, circular, uncoated, flat-faced, bevelled edged, matt finished tablets, with a break line on one side and plain on the other side.
- Yellow, circular, flat, bevelled, uncoated tablets with a central break-line on one side and plain on other side.
- Yellow-coloured, circular, flat, bevel-edged uncoated tablets with break-line on one surface and plain on 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.



# Case Study 2

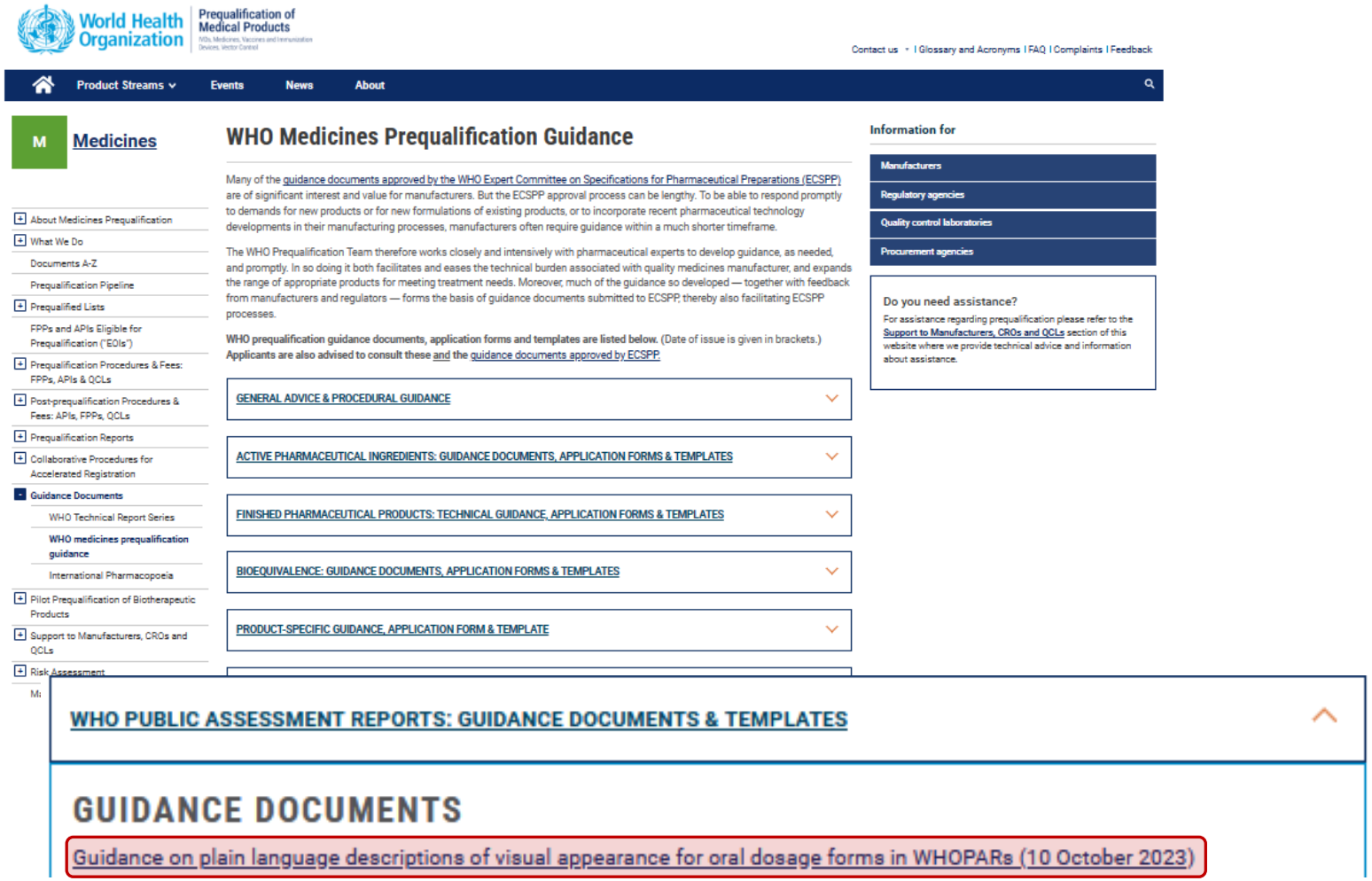
- Hard ovoid calcium carbonate capsule, buff to coffee-coloured, containing gallinaceous DNA in a spherical jasmine to gamboge-coloured lipoprotein delivery system suspended in a clear, viscous albuminaceous support solution.

- 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 - Background

**Constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.**

- Functional or non-functional, for example:
  - colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring aromatic substances and diluents
  - also constituents of the outer covering of the medicinal products – gelatine capsules, rectal capsules, coating material or constituents of the printing ink
- Some with recognised action or effect in certain circumstances

→ **Warning statements relating to their presence in medicinal products**

# 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

**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."

Two exceptions

- Lactose
- Sodium

# Excipients – Lactose (I)

**EU –Guideline** *SmPC proposal*

*(Threshold zero):*
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*(Threshold 5g):*
Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.

## Differentiation

- Galactose intolerance
- Total lactase deficiency
- Glucose-galactose malabsorption
- Lactose intolerance
- Cow's milk-protein allergy

# Excipients – Lactose in the WHOPARs

- ***Lactose wording concerning serious (congenital) genetic disorders*** *(Threshold zero)*

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

- ***Lactose wording concerning lactose intolerance***

*(Threshold < 400 mg per dose)*

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance <*if the wording for genetic disorders above is also included, add* 'in other patients'>.

*(Threshold > 400 mg per dose)*

The small amount of lactose in each dose may cause symptoms of intolerance<*if the wording for genetic disorders above is also included, add* 'in other patients'>.

# Excipients – Lactose in the WHOPARs

- ***Lactose wording concerning cow's milk protein allergy***

  *(Threshold zero; only applicable to lactose of bovine origin)*

  *for products given orally:*

  Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

  *for products given parentally:*

  Patients who are allergic to cow's milk must not be given this medicine as it may contain trace amounts of cow's milk protein.

- ***Lactose wording concerning diabetes***

  *(Threshold 5 g per dose)*

  Lactose is a source of glucose. Patients with concurrent diabetes should take account of the amount of lactose in this medicine *(x in each <dosage unit>).*

# Excipients - Sodium

**EU –Guideline** *SmPC proposal*

(*Threshold <1 mmol (23 mg) per dose)*

This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit><unit volume>, that is to say essentially 'sodium-free'.

*(Threshold ≥1 mmol (23 mg) per dose)*

This medicine contains x mg sodium (main component of cooking/table salt) in each <dosage unit><unit volume>.
This is equivalent to y% of the recommended maximum daily dietary intake of sodium for an adult.

Information to come under subheading

"Excipients with potential clinical effect"

# Excipients – Sodium in the WHOPARs

***Section 2 SmPC***

***"Excipients with potential clinical effect"***

Heading and warning only included if product contains 1 mmol (23 mg) sodium or more.

***Section 6.1 SmPC***

***"List of excipients"***

If the medicine is 'essentially sodium free', i.e. contains excipients with sodium but the total quantity of sodium is less than 1 mmol (23 mg) per dosage unit, a statement in section 6.1 is included:

"This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per <dosage unit, e.g. tablet>."

# Non-functional excipients – e.g. colourants

**Use of these excipients in medicinal products may lead to:**

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

→ **Highlighting this aspect, e.g. in WHOPAR part 1, is currently being discussed.**

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

# 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, the WHOPARs for products prequalified based on SRA approval will be supplemented by a “WHO-PQ recommended patient information leaflet” (as part 3a), a “WHO-PQ recommended summary of product characteristics” (as part 4a) and “WHO-PQ recommended labelling” (as part 5a), as applicable.”

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

# News on „SRA-WHOPARs“

**Note (ff)**

- Parts 3a and 4a will be based on the relevant current WHO treatment guidelines and are regarded necessary for the use of the product in populations, settings or regions relevant for distribution of the product based on its prequalification status.
- Parts 3a, 4a and 5a will include the WHO recommended storage condition with shelf life where appropriate. Note that WHOPAR parts 3a, 4a and 5a will not replace the SRA approved product information, but will be provided as supplemental information.”


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