Prequalification of medicines

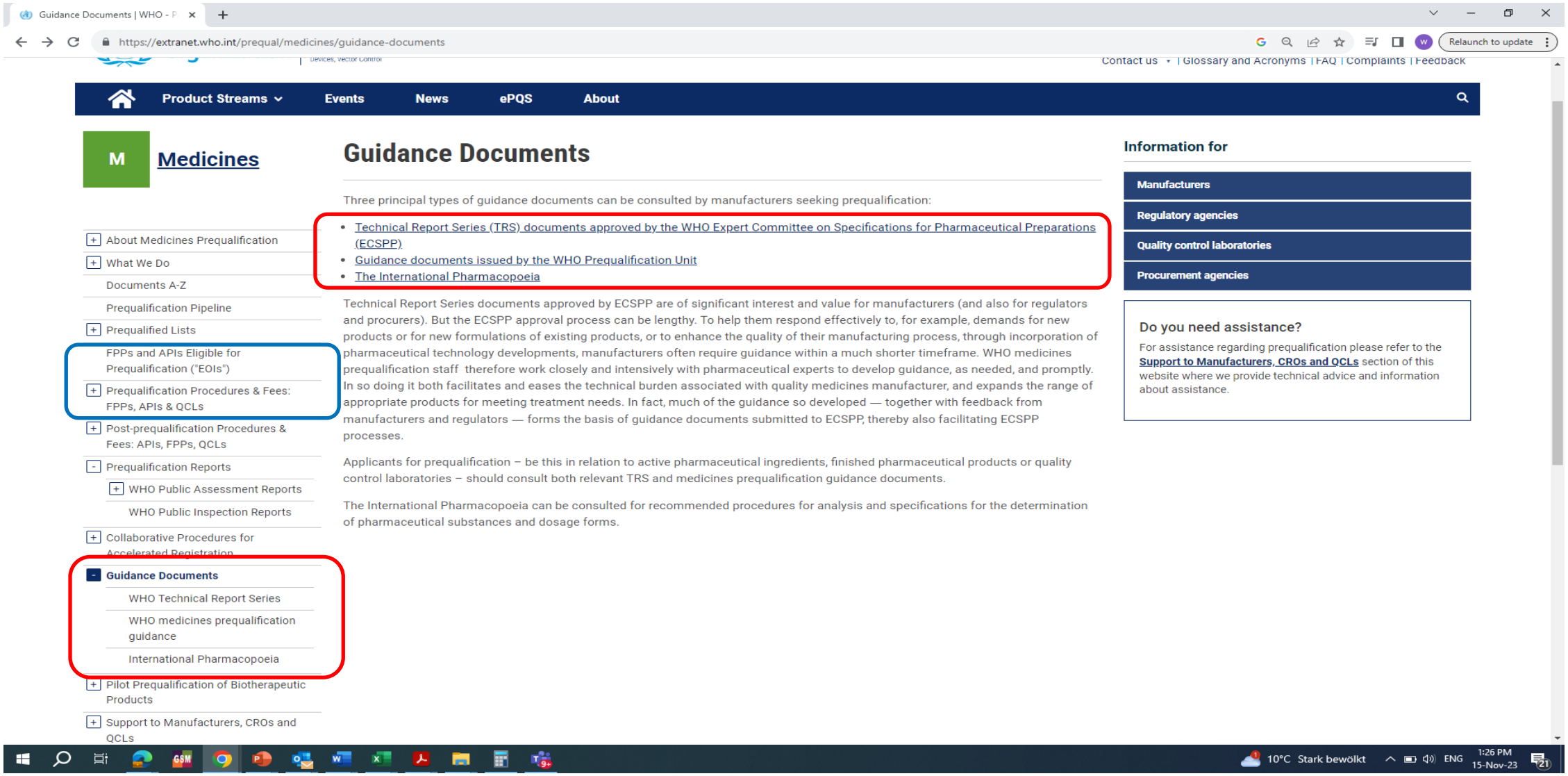
FPP quality: a quick overview and updates

Wondiyfraw Worku
Lead QA assessor

Prequalification pathways

- The full assessment procedure
  - For generics, based on submission of a full CTD dossier and assessment by PQT/MED
  - If desired by applicants, this path may also apply for products approved by SRAs/WLAs (facilitated by access to SRA/WLA unredacted assessment reports)
- The abridged assessment procedure
  - For innovator and generic products approved by SRAs/WLAs - full reliance procedure

Guidelines


Guidance Documents | WHO - P
https://extranet.who.int/prequal/medicines/guidance-documents
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Prequalification Pipeline
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FPPs and APIs Eligible for Prequalification ("EOIs")
Prequalification Procedures & Fees: FPPs, APIs & QCLs
Post-prequalification Procedures & Fees: APIs, FPPs, QCLs
Prequalification Reports
WHO Public Assessment Reports
WHO Public Inspection Reports
Collaborative Procedures for Accelerated Registration
Guidance Documents
WHO Technical Report Series
WHO medicines prequalification guidance
International Pharmacopoeia
Pilot Prequalification of Biotherapeutic Products
Support to Manufacturers, CROs and QCLs
Guidance Documents
Three principal types of guidance documents can be consulted by manufacturers seeking prequalification:
Technical Report Series (TRS) documents approved by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)
Guidance documents issued by the WHO Prequalification Unit
The International Pharmacopoeia
Technical Report Series documents approved by ECSPP are of significant interest and value for manufacturers (and also for regulators and procurers). But the ECSPP approval process can be lengthy. To help them respond effectively to, for example, demands for new products or for new formulations of existing products, or to enhance the quality of their manufacturing process, through incorporation of pharmaceutical technology developments, manufacturers often require guidance within a much shorter timeframe. WHO medicines prequalification staff therefore work closely and intensively with pharmaceutical experts to develop guidance, as needed, and promptly. In so doing it both facilitates and eases the technical burden associated with quality medicines manufacturer, and expands the range of appropriate products for meeting treatment needs. In fact, much of the guidance so developed — together with feedback from manufacturers and regulators — forms the basis of guidance documents submitted to ECSPP, thereby also facilitating ECSPP processes.
Applicants for prequalification – be this in relation to active pharmaceutical ingredients, finished pharmaceutical products or quality control laboratories – should consult both relevant TRS and medicines prequalification guidance documents.
The International Pharmacopoeia can be consulted for recommended procedures for analysis and specifications for the determination of pharmaceutical substances and dosage forms.
Information for
Manufacturers
Regulatory agencies
Quality control laboratories
Procurement agencies
Do you need assistance?
For assistance regarding prequalification please refer to the Support to Manufacturers, CROs and QCLs section of this website where we provide technical advice and information about assistance.
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Main quality guideline

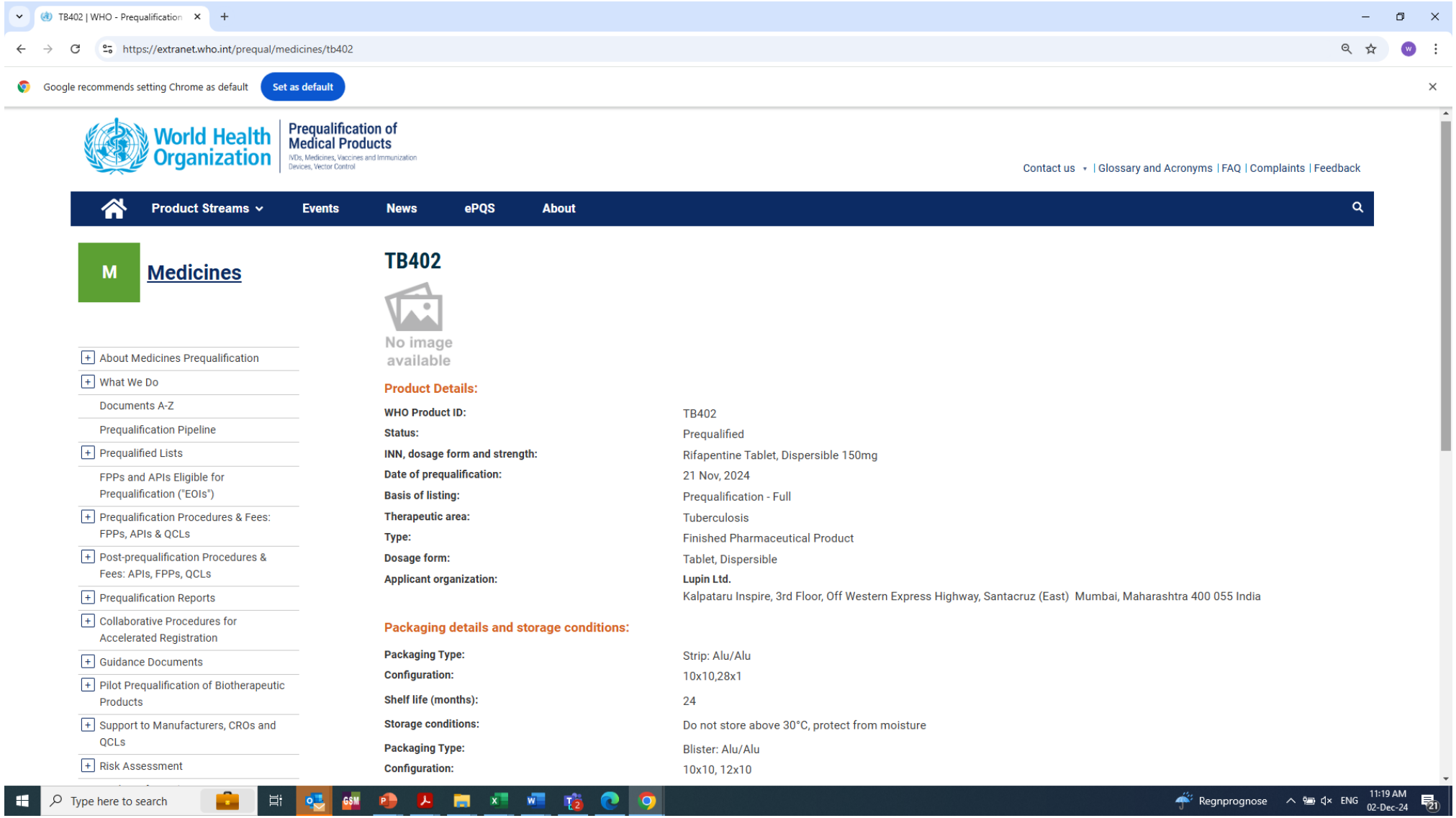
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part – TRS 970, Annex 4

  - Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format – TRS 961, Annex 15

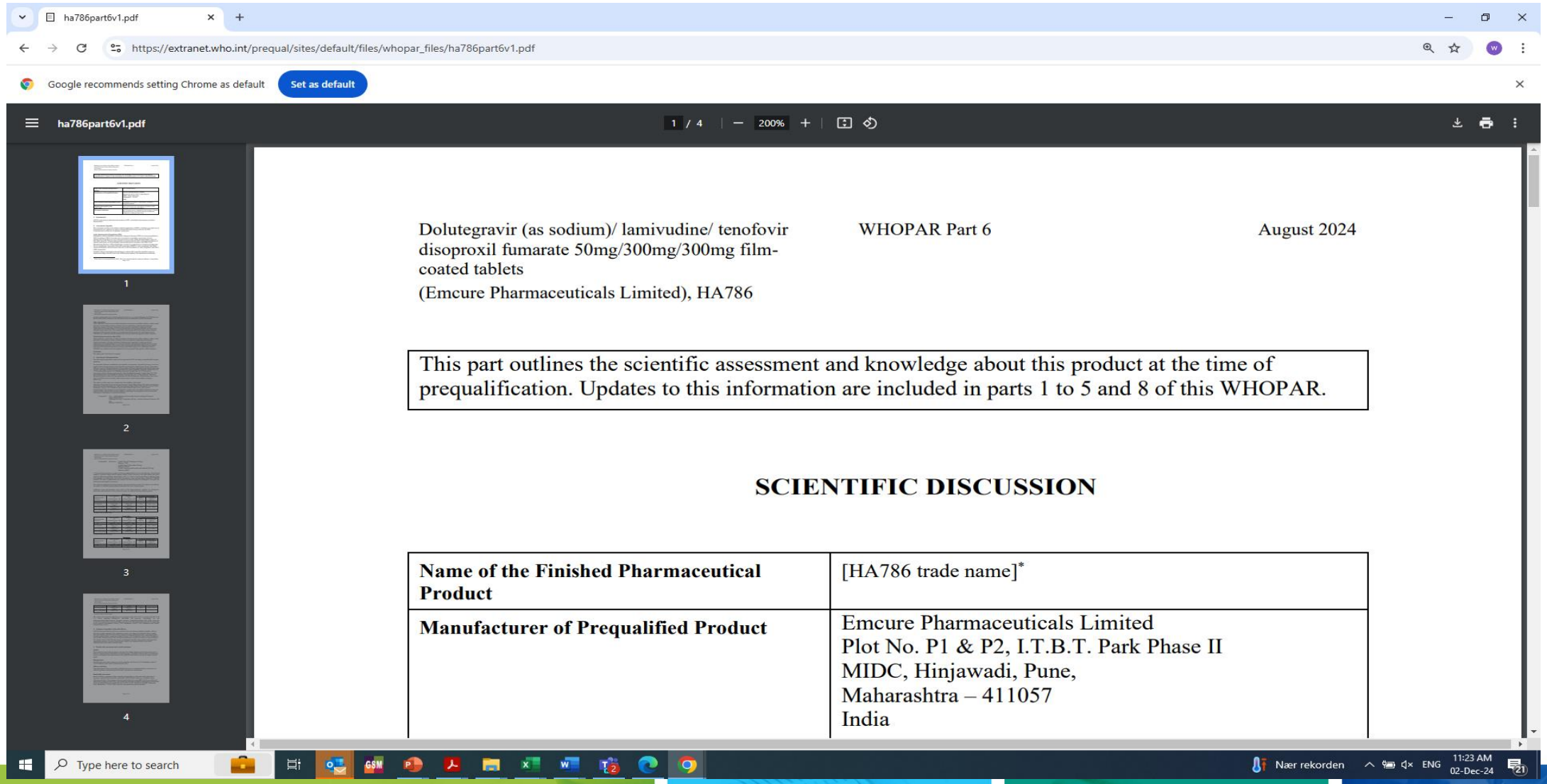
Additional guidance/clarification documents

- ✓ Additional guidance on submission requirements for medroxyprogesterone acetate depot injection products using the Common Technical Document (CTD) format
- ✓ Common Deficiencies in Finished Pharmaceutical Product (FPP) Dossiers - Additional Guidance for Manufacturers
- ✓ FAQ: Prequalification of medicines for reproductive health
- ✓ Product specific additional guidelines

Public information on prequalified products



Public information on prequalified products



Model dossier

WHO Model Dossier

The Model Dossier (MD). The MD is an example medicine dossier. The product chosen for the MD is a prequalified solid oral product, levonorgestrel 0.75 mg tablets. However, the MD is intended to have general applicability across therapeutic areas and can be broadly useful, including for example to new drugs.

Note: To download the Model Dossier, you will be required to agree to our disclaimer and submit your contact information.

Download Model Dossier

(Zip 52mb)

To see more information about this visit this section

Upcoming updates to the QOS-PD/QIS

- API CPQ date
  - section 2.3.S.2.1 will require indicating date of the current CPQ
- Declaration regarding residual solvents content of the FPP
  - A declaration box in 2.3.P.5.5 will be added to ensure that applicants have considered all residual solvents that may be potentially present in the FPP and that the product complies to ICH Q3C.
- QSAR expectation (per ICH M7) for new inhouse impurities observed in the FPP – in 2.3.P.5.5

N-nitrosamines

Rifampicin and rifapentine products:

- We have continued accepting interim limits for rifapentine and rifampicin products

Other at-risk products (FPPs with vulnerable amine containing APIs):

- Applicants of prequalified products are being requested to update previously concluded risk assessments and undertake confirmatory testing based on a prioritized approach considering:
    - likelihood of formation of nitrosamines,
    - potency of the impurity (based on CPCA) and
    - treatment duration

N-nitrosamines – potentially at-risk products

Under assessment applications

- Applicants are being requested to update their risk assessment exercises and undertake confirmatory testing before prequalification or within a defined time following prequalification

Not yet submitted applications

- Applicants are expected to undertake risk assessments according to the latest guidance and recommendations knowing that nitrites/nitrates are common findings in major excipients
    - Confirmatory testing, when needed, must be conducted before submission
    - If required, mitigation strategies should also be implemented before submission
    - PQT/MED is open for a case-by-case justifications/discussions

N-nitrosamines – potentially at-risk products

- **Acceptance criteria:** based on approaches agreed at the NITWG/NISG collaborations with other agencies:

  - Using TD50 values if substance specific acceptable animal carcinogenicity data exist
  - Otherwise,
    - Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines
    - A negative result in an GLP-compliant enhanced Ames test (EAT
    - TD50 based on a surrogate nitrosamine for which acceptable carcinogenicity data is available
    - A negative result in a relevant well-conducted in vivo mutagenicity study

N-nitrosamines – risk mitigation strategies

Applicants should explore ways of reducing or eliminating the presence of N-nitrosamines in pharmaceuticals:

- Screening of major excipients for nitrite/nitrate contents and finding suitable replacements with “low” nitrite/nitrate content
- Protective measure during manufacture and storage
- Modifying formulations to incorporate antioxidants or microenvironment pH modifying agents
- FDAs recently issued guide: *Control of Nitrosamine Impurities in Human Drugs* provides useful guidance regarding risk factors and mitigation strategies (e.g., biowaiver considerations for reformulations)

DEG and EG impurities – a reminder

- The generic guide requires that excipients comply to the available Pharmacopeial monographs in BP, Ph.Eur., Ph.Int., USP and JP

- Applicants should ensure that at risk excipients comply to the current pharmacopeial requirements

- For example, USP-NF monographs for at risk excipients are being updated on an ongoing basis

❖ control of DEG and EG levels as part of identification test (e.g., glycerin)
❖ control as part of impurities section of the monograph (e.g., PEG 4000)
❖ control per USP<469> (e.g., polysorbate 20)

Recommendations – full assessment

- Identifying and addressing major issues before submission, e.g.,

  - Batch to batch consistency issues observed during process qualification on primary batches
  - Out of specification stability results on primary batches

- Engaging with API suppliers to ensure timely APIMF progress (when referring to not yet accepted APIMFs)

Recommendations - variation assessments

- The *FAQ: Variations* document is being updated to provide guidance on changes which are not addressed in the main guide.
- Particular attention should be given to additional considerations/requirements for API-related changes (changes in API source or API manufacturing process) outlined in the FAQ document.
- All changes should be evaluated in terms of impact on nitrosamine contamination; the variation application form has been updated requiring applicants to declare that proposed changes do not increase nitrosamines risk.

Recommendations – Requalification assessments

1. *FPP manufacturers not always informed about API changes;* Manufacturer of API should always keep FPP manufacturers updated of changes.
2. *Many manufacturers don't submit APQR for non-commercialized products;* PQRs should be prepared irrespective of whether the product has been manufactured or not (consult TRS986, Annex 2)
3. *Unsolicited changes;* We see a lot of unsolicited changes to documents submitted through requalification, rather than the variations procedure. Only AN are allowed to be submitted during requalification.
4. *Samples not submitted on time;* Applicants should ensure that samples are promptly dispatched after submission of RQ documents.

Recommendations – SRA status verification reviews

- *Applicants are not notifying PQT/MED timeously of variations accepted by the reference SRA*. PQT/MED should be notified of such approvals immediately (and not as part of the SRA status verification process)

- *Applicants tend to delete the "for WHO use" section of the QIS inserted by PQT/MED on prequalification.* This section should not be modified or deleted. If a change is needed it should be separatley indicated

We would like to hear from you

- We welcome your comments and feedbacks on our requirements, procedures, assessment policies and approaches
- Tell us where you think additional guidance or clarifications would be useful
- Do not hesitate to approach us if you require clarifications regarding our *request for further information* letters
- Use opportunities for pre-submission meetings and other one-to-one meetings but also email interactions

Thank you