Prequalification of medicines

Updates - FPP quality

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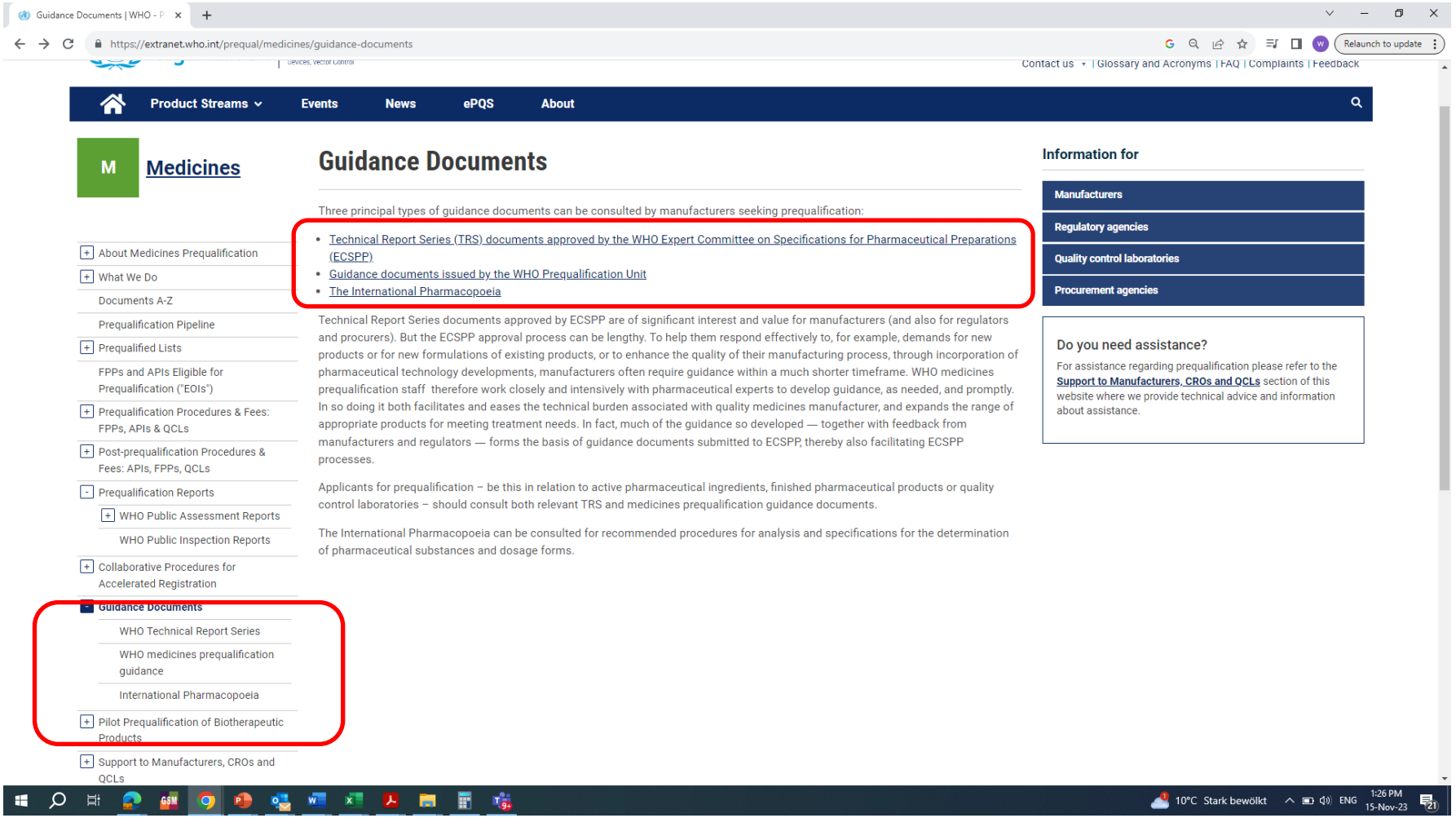
Talk points

- ✓ A quick intro to prequalification pathways and quality guidelines
- ✓ A few updates
  - ✓ Continuous manufacturing – PQT/MED approach
  - ✓ Nitrosamines – updates
  - ✓ DSV calculation for the Q purposes
- ✓ Ways to facilitate assessment and reduce deficiencies/assessment rounds

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, also for products approved by SRAs (facilitated by access to SRA unredacted assessment reports)
- The abridged assessment procedure
  - For innovator and generic products approved by SRA - full reliance procedure

Guidance documents



Main quality guideline

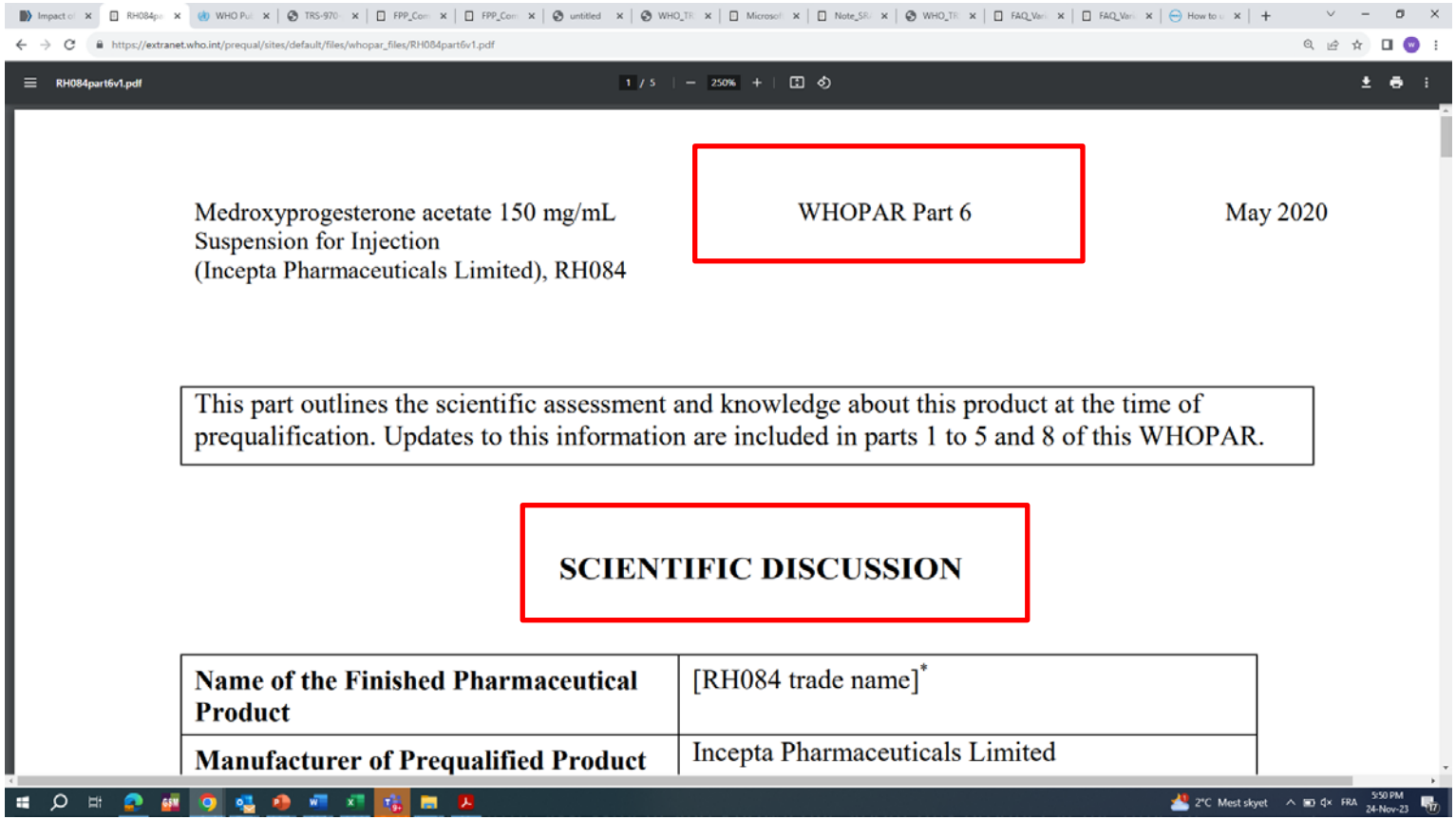
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part – TRS 970, Annex 4

  - 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

Some of the additional quality 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

information on prequalified products



RH084part6v1.pdf

Medroxyprogesterone acetate 150 mg/mL Suspension for Injection (Incepta Pharmaceuticals Limited), RH084

WHOPAR Part 6

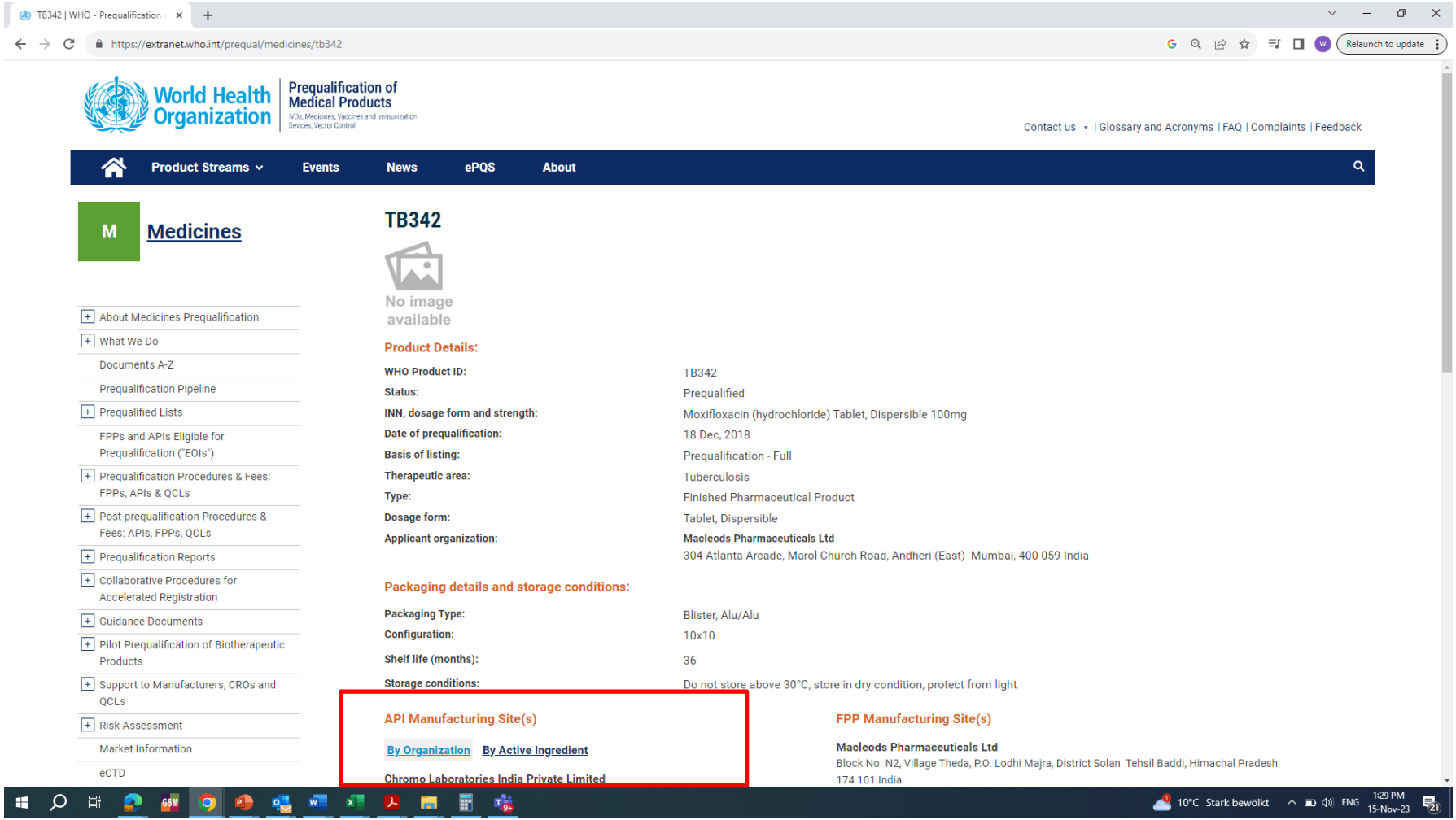
May 2020

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[RH084 trade name]*
Manufacturer of Prequalified Product	Incepta Pharmaceuticals Limited

Public information on prequalified products



The abridged prequalification procedure

- For products approved by an SRA – a full reliance procedure
  - *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* – Annex 5 TRS 986
    - documentation to establish sameness with the SRA approved product required
    - CTD dossier is not required
- Additional guidance documents:
  - stability data requirements
  - provision for a WHO PQT/MED recommended product information additional to the SRA approved product Information
- Close 200 products prequalified via this procedure (currently listed 107 products)

Variations

- Main variations guideline:

https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?isAllowed=y&sequence=1#page=107&zoom=auto,-501,678

- Procedure and timelines:
  - https://extranet.who.int/prequal/medicines/multisource-generic-fpps
- Frequently asked questions document, including
  - Additional guidance on variation applications concerning nitrosamine impurities
  - Examples of changes reclassified as minor or notification
  - Examples of changes to be implemented within GMP change control
- https://extranet.who.int/prequal/sites/default/files/document_files/FAQ_Variations-revision_15Dec2022.pdf
- FAQ periodically updated for example to reclassify change types

Requalifications

- Requalification occurs every 5th year or earlier if necessary
- Any annual notifications not notified at the time of RQ submission (or during RQ submission) should be included in the submission package.
- Going forward, SRA status verification for products prequalified via the abridged procedure will be done routinely (every five years or earlier if necessary).

Continuous manufacturing (CM)

- CM promises not only increasing manufacturing efficiency but also improving processes and controls through greater use of technology
- PQT/MED welcomes collaborations with applicants who wish to convert current process to CM or develop a new products based on CM:
  - If CM concerns less critical single steps only, such as film coating,
    - ✓ submission as variation possible
  - If CM involves one or more critical processing steps,
    - ✓ a pre-submission discussion, based on a briefing document prepared taking into consideration the ICH Q13 considerations, requirements and available data, would be required

Nitrosamines – assessment policy

- Current assessment policies for APIs and FPPs are available at:

https://extranet.who.int/prequal/node/1326

https://extranet.who.int/prequal/sites/default/files/document_files/Guidance_Nitrosamine_Contamination_Policy_APIs_Rev1_0.pdf

  - Risk assessments must be completed before dossier submission
  - Risk assessments should be revisited when changes are introduced, or as new information becomes available
  - Confirmatory testing, when a risk is identified, should occur before submission

Note: we may request updated risk assessments and confirmatory testing based on new information that becomes available to us

Nitrosamines – rifampicin products

- PQT/MED continued accepting interim limits at or below 5ppm for MeNP impurity
- However, the expectation is that the AI or a further reduced interim limit will have been achieved by end of the year.
- In early 2024, we will review progresses and contact concerned applicants

Nitrosamines – rifapentine products

- PQT/MED continued accepting interim release limits at or below 20ppm for CPNP impurity.
- For prequalified and under assessment products, we expect continued efforts towards achieving the AI or tightened interim limits
- For products under development, formulation and process developments should focus on achieving the AI or significantly lower levels than current interim limits
  - Impact of different types and amounts of anti-oxidants in the formulation,
  - Measures of protections of intermediate products from oxidation during processing
  - High moisture/air barrier container closure system

Nitrosamines – AL products

- Routine controls for NDBA are being placed for the prequalified and under assessment products based on the AI (26.5ng/day)
- monitoring of levels in stability samples needs to continue
- For products under development,
  - considerations should be made in selecting nitrite free excipients
  - routine control of n-DBA in Lumefantrine API may also need to be considered
  - primary stability batches should be monitored using a fully validated method

Nitrosamines – other at-risk products

- FPPs with vulnerable amine containing APIs
- for most products, risk assessments were concluded with “no risk found” outcomes
- however, given the various risk factors and continued finding of NDSRIs* in suspected products, confirmatory testing of all FPPs containing vulnerable amines should now be considered
- requests, for completing confirmatory tests for the relevant PQD and under assessment products within a specified time, to be sent out

*NDSRIs: Nitrosamines drug substance related impurities

Nitrosamines – other at-risk products: timelines for completion of confirmatory testing

- Different timelines to be set based on consideration of
  - Potency categorization of the suspected NDSRI per the CPCA*
  - Treatment duration

*CPCA: *Carcinogenic Potency Categorization Approach for N-nitrosamines (CPCA),* and the related document *Enhanced Ames test conditions* were prepared by NITWG safety working group and adopted by participating regulatory agencies including PQTMED

Dose to solubility (DSV) calculation for quality review – an update

- According to the generic guide (Annex 4, TRS 970), DSV for purposes of the quality review is defined as

$$DSV = \frac{\textbf{highest dose strength (mg)}}{\text{minimum concentration of API (mg/mL) from solubility data}}$$

- However, inline with the latest solubility definitions provided in other WHO guidelines and ICH M9, going forward, DSV, for the quality purposes should be computed as follows:

$$DSV = \frac{\textbf{highest single therapeutic dose (mg)}}{\text{minimum concentration of API (mg/mL) from solubility data}}$$

What may facilitate assessment and so reduce questions?

- Characterization of the BE batch for all critical process parameters and attributes (inc dissolution profiles) at the time of release
- Reviewing process parameters and controls proposed for production batches before submission (to ensure representatives of the BE and other primary batches)
- Providing specific discussions on how process parameters for production batches are determined (scale up considerations), including a justification for the width of proposed ranges as applicable

What may facilitate assessment and so reduce questions?

- Proactively discussing differences (and any related impact) in equipment, process parameters and controls for production batches vs the process executed for the biobatch
- Proactively identifying any trends, out of trend, at or close-to-limit results and investigating the observation if warranted, and providing a related discussion in the dossier
- Frequent engagement with API suppliers to facilitate timely response submission for APIMF questions (a rate limiting factor in some cases)
- Take opportunities, such as PSM and e-mails, to bring up possible issues before submission

Your comments and feedbacks

- We welcome your comments and feedback 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 on our deficiency letters and if you wish to contest our requests.

Thank you