

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

Guidance Documents | WHO - P x +

https://extranet.who.int/prequal/medicines/guidance-documents

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M Medicines

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 \(ECSP\)](#)
- [Guidance documents issued by the WHO Prequalification Unit](#)
- [The International Pharmacopoeia](#)

Technical Report Series documents approved by ECSP are of significant interest and value for manufacturers (and also for regulators and procurers). But the ECSP 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 ECSP, thereby also facilitating ECSP 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.

Guidance Documents

- WHO Technical Report Series
- WHO medicines prequalification guidance
- International Pharmacopoeia
- Pilot Prequalification of Biotechnological Products
- Support to Manufacturers, CROs and QCLs

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

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https://extranet.who.int/prequal/sites/default/files/whopar_files/RH084part6v1.pdf

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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

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Public information on prequalified products

Browser: TB342 | WHO - Prequalification | x | +
 URL: https://extranet.who.int/prequal/medicines/tb342

World Health Organization | Prequalification of Medical Products
 (Vaccines, Medicines, Vaccines and Immunization Devices, Vector Control)

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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

TB342

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Product Details:

WHO Product ID:	TB342
Status:	Prequalified
INN, dosage form and strength:	Moxifloxacin (hydrochloride) Tablet, Dispersible 100mg
Date of prequalification:	18 Dec, 2018
Basis of listing:	Prequalification - Full
Therapeutic area:	Tuberculosis
Type:	Finished Pharmaceutical Product
Dosage form:	Tablet, Dispersible
Applicant organization:	Macleods Pharmaceuticals Ltd 304 Atlanta Arcade, Marol Church Road, Andheri (East) Mumbai, 400 059 India

Packaging details and storage conditions:

Packaging Type:	Blister, Alu/Alu
Configuration:	10x10
Shelf life (months):	36
Storage conditions:	Do not store above 30°C, store in dry condition, protect from light

API Manufacturing Site(s)

[By Organization](#) [By Active Ingredient](#)

Chromo Laboratories India Private Limited

FPP Manufacturing Site(s)

Macleods Pharmaceuticals Ltd
Block No. N2, Village Theda, P.O. Lodhi Majra, District Solan Tehsil Baddi, Himachal Pradesh
174 101 India

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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).

- 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

- 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

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

- 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:

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

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