Active Pharmaceutical Ingredient assessment

Medicines Assessment Team

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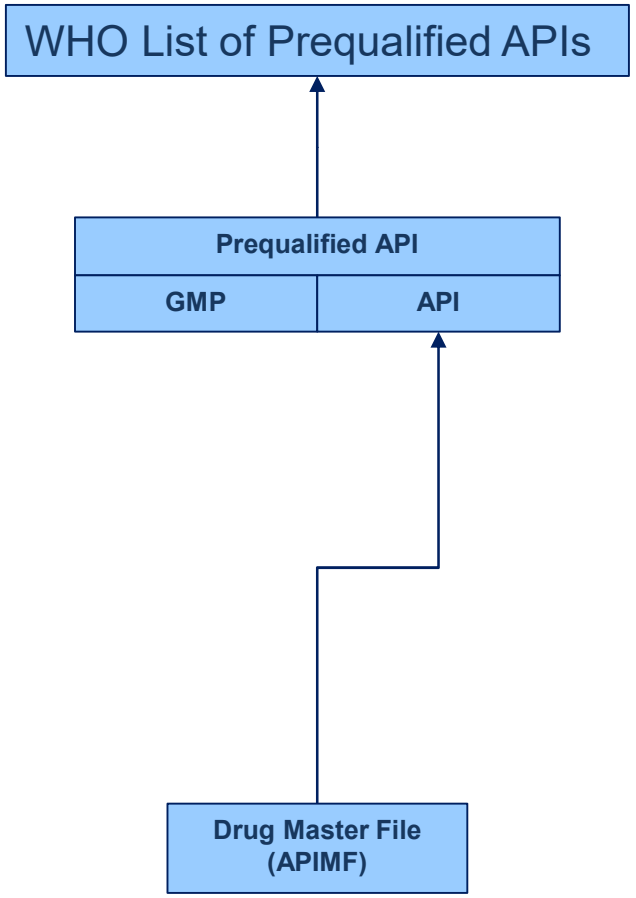
API assessment within PQT Medicines

API manufacturers may be involved in two ways.

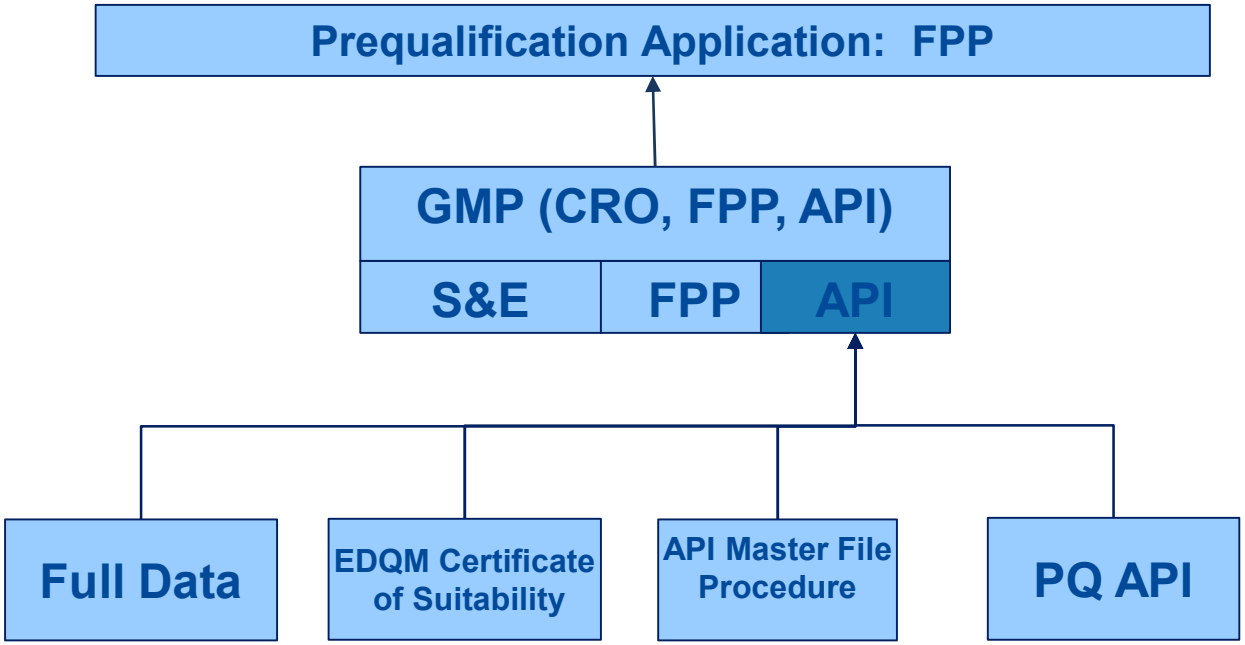
- Seeking prequalification of their own API.
- In support of a finished pharmaceutical product (FPP) seeking prequalification (4 options).

Prequalification of APIs

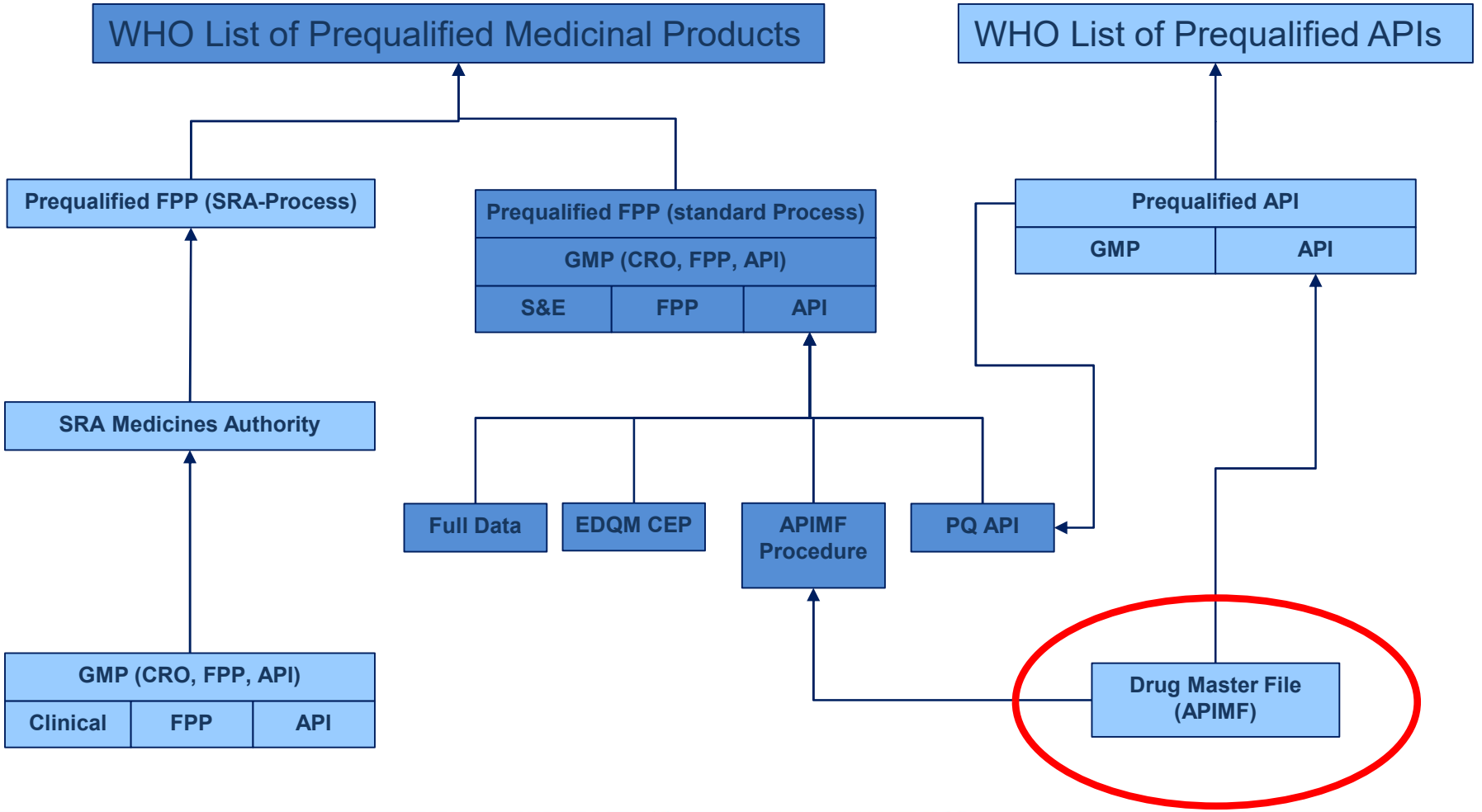
- APIs can be prequalified independent of an FPP application.
- Public recognition as a source of quality API, manufactured in compliance with GMP.
- Serves as a point of difference between good quality and poor quality APIs.
- Opportunities to verify compliance with GMP.
- Opportunities to compile, revise and refine their regulatory documentation, leading to quicker acceptance by other national regulatory agencies.
- API PQ is increasingly recognised by National authorities.



API Manufacturers supporting an FPP



Prequalification of APIs



API activities

- Currently 156 Prequalified APIs

In addition, a further 81 APIMFs accepted for the APIMF procedure only

- 34 APIs under assessment for Prequalification

In addition, a further 15 APIMFs under assessment for the APIMF procedure only

- 179 amendment applications completed in 2021 (15% more than in 2020)

API PQ assessment in 2021

First rifapentine, clofazimine and dexamethasone APIs prequalified.

Expedited review of the first 4 molnupiravir API applications started.

Overall, however an increase in WHO and manufacturer time for API PQ in 2021.

WHO increase in time due to:

- Development of new IT system
- Increase of amendment applications
- Impact of Covid-19 pandemic
- Nitrosamines follow-up

Topics of interest- API assessment

Covid-19

Nitrosamine impurities

Covid-19- Impact

Greater flexibility for requests to extend deadlines for application responses in 2021.

Availability of external assessors reduced in 2021.

Due to teleworking arrangements- API applications should be sent via a secure link to an online document repositories (APIassessment@who.int).

Covid-19- API Applications

Invited APIs: baricitinib, dexamethasone, molnupiravir and nirmatrelvir.

Expedited review.

Reduced stability data at submission acceptable with a commitment to provide ongoing stability data on a rolling basis.

Status of Covid-19 API applications in:

https://extranet.who.int/pqweb/key-resources/documents/status-covid-19-medicines-and-apis

Nitrosamine impurities

Manufacturers to review all their processes to look for nitrosamine impurities (risk evaluation)-April 2020

https://extranet.who.int/pqweb/news/manufacturers-conduct-risk-assessments

If a risk identified, manufacturers expected to test whether nitrosamines detected.

If nitrosamines present, manufacturers need to:

- Investigate the root-cause;
- Implement changes to prevent them or to reduce to acceptable intake limit (mitigation measures). May require time until they can be verified as effective and applicable at a larger scale.

Nitrosamine impurities-APIMFs

Accepted APIMFs:

- Risk evaluation has been conducted for all accepted APIMFs following PQT/MED's request to conduct risk assessments (April 2020).

- Confirmatory tests (when risk identified) and mitigation measures ongoing for some APIMFs.

New APIMFs:

- Risk evaluation to be conducted prior submission and report to be appended to the APIMF (whether a risk is identified or not).

Nitrosamine impurities- FPPs

Prequalified FPPs:

- Risk evaluation has been conducted for nearly all FPPs following PQT/MED's request to conduct risk assessments (April 2020).
- Confirmatory tests (when risk identified) and mitigation measures ongoing for a few FPPs.

New submissions:

- Risk evaluation to be conducted prior to submission and a declaration to be provided in the dossier. Submission of the risk assessment report required only if a risk is identified or when requested by assessors.

Rifapentine and rifampicin products

FAQ_Nitrosamine_18Dec2020.pdf (who.int)

Benefit/risk balance decisions & interim limits

Critical products:

- When risk of not taking the treatment outweighs risk associated with the nitrosamine impurity, higher limits can be accepted on a temporary basis (interim limits).

- This requires an in-depth quality assessment and close monitoring from regulators:
  - interim limit set as low as possible
  - mitigation measures applied as soon as possible

Rifapentine and rifampicin products

Nitrosamine impurities were identified (CPNP and MeNP, respectively).

Expected to be present at varying levels in all rifapentine and rifampicin products.

PQT/MED benefit/risk assessment: risk associated with interruption of treatment far outweighs any potential future cancer risk associated with the nitrosamine impurity.

Higher interim limits on a temporary basis, while defined mitigation measures are put in place by the companies.

Company mitigation measures may require time.

Rifampicin products

PQT/MED requested in Sep 2020 all manufacturers of rifampicin products (APIs and medicines) to test the nitrosamine impurity in a representative number of batches.

Results provided for all prequalified APIs and FPPs show that MeNP is present at trace levels in all batches tested (below or close to 5 ppm).

Interim limits for MeNP impurity based on risk benefit considerations and process capability on a case-by-case. Will be reviewed regularly.

PQT/MED is closely monitoring ongoing work by manufacturers (mitigation measures).

PQT/MED's recommendation not to interrupt any rifampicin treatment remains.

https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

Rifapentine

Priftin:

Prequalification based upon the registration of the medicine with US FDA (i.e. based on approval by a stringent regulatory authority).

PQT/MED recognises US FDA decisions (interim limit).

Generics (under assessment):

Similar interim limits being considered based on risk benefit considerations and process capability.

Nitrosamines impurities

Approach from industry and regulators continues to evolve.

Guidance on root causes, control and mitigation measures in EMA and US FDA websites:

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

PQT/MED's approach harmonized (US FDA, EDQM, EMA…).

PQT/MED collaboration with other regulators (e.g. Nitrosamines International Strategic Group).

Thank you

- For API related questions please do not hesitate to contact us
  - Fakea@who.int, cc stahlm@who.int