Prequalification requirements and anti-hepatitis C medicines

Mr. Wondiyfraw Worku
Assessor, WHO Prequalification Team- Medicines
topics

- Scope and experience of PQ
- Prequalification process
- Invitation for expression of interest (EOI)
- Reflection on anticipated prequalification requirements for anti-hepatitis C products
WHO Prequalification

- A United Nations Programme managed by WHO
  - Prequalification of medicines,
  - Prequalification of vaccines,
  - Prequalification of diagnostics
- Identify products which are acceptable in principle for procurement by UN and other agencies
- To assist manufacturers and NMRAs
- The three product streams have recently been merged to achieve synergies
Prequalification of Medicines

- Started in March 2001 as a Pilot Project: Focus on HIV/AIDS
- Partners included WHO, UNICEF, UNFPA, UNAIDS and supported by World Bank
- Quickly expanded to include Tuberculosis, Malaria, Reproductive Health, Influenza and others
- Funded by donors – mainly UNITAID and Bill and Melinda Gates Foundation
- Assessments and Inspections are done together with national experts from Stringent (ICH) and emerging regulatory authorities
Scope of Medicines prequalification

- Limited to priority medicines (and APIs) as published in Invitations for Expression of Interest (EOI on PQP website)

- Medicines eligible for prequalification determined by WHO disease oriented programmes (“perceived medical need”)

- Mostly generics and so far only “chemical” drugs

- Only products are prequalified!
Current therapeutic areas

- Therapeutic areas invited:
  - HIV/AIDS
  - Malaria
  - Tuberculosis
  - Reproductive Health
  - Influenza
  - Acute diarrhoea in children (zinc)
  - Neglected Tropical Diseases (NTDs)

- Potentially other categories of products, if there is the need
Routes to prequalification

- **Full dossier route**
  - Via review of full quality and safety/efficacy (BE) data
  - Inspection of all sites involved

- **SRA route (abbreviated route)**
  - Based on MA already granted by SRA
  - Full dossier not required
  - Sites compliance usually verified through desk review of available evidence
Prequalification process

- Expression of Interest
- Product dossier SMF
- Assessment
- Additional information and data
- Acceptable
- Prequalification
- Inspections
- Corrective actions
- Compliance
- Maintenance and monitoring
Expression of Interest (EOI)

- A list containing medicines invited for prequalification
- List developed by WHO clinical departments based on perceived medical need (public health importance) and inclusion in a WHO treatment guideline and/or WHO essential medicines list
- The list is updated whenever needed
Anti-hepatitis C medicines included in current WHO treatment guide- April 2014

- Biotechnology product
  - PEG-interferon (PEG-IFN) - a polypeptide

- Chemical drugs
  - Ribavirin
  - Sofosbuvir
  - Simeprevir
  - Telaprevir
  - Boceprevir

- None of the above are currently invited but the relevant clinical department within WHO may decide to include some or all
Anti-hepatitis C products
Anticipated prequalification requirement: SRA route

- Applicable for innovator, generic and biosimilar products approved by SRA

- Guideline and submission procedure available on PQP website

Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities
Anticipated prequalification requirements
Full dossier route - Generics

- Applicable for generics of Ribavirin, Telaprevir, Boceprevir, Sofosbuvir and Simeprevir (chemical drugs)

- API and FPP quality should be documented in accordance with the generic guide (Annex 4, TRS 970).

- Safety/efficacy (via BE study) should be established (Annex 7 and 8 of TRS 937)
  - Acceptable comparator products will be announced (in each case, reference product approved by SRA exists)
  - Specific advice on BE design and review of BE study protocol can be provided by PQ when the medicines are included in the EOI
Anticipated prequalification requirements
Full dossier route - PEG-IFN

- Unlike generics, PEG-IFN and other biosimilars (and their reference products) need to be characterized for example with respect to:
  - Amino acid sequence,
  - Higher structures including aggregation
  - Post translational modifications
  - Chemical modifications such as PEGylation
  - Others such as protein deamidation

- Such characterization requires use of state-of-the art analytical methodologies and specific expertise

- Comparability in terms of non-clinical and clinical information also needs to be demonstrated

- PQ currently does not have specific guidelines and has no experience of such products
  - However, available guidelines as issued by WHO and SRA can be used
Available guidelines

- WHO’s Guideline on Evaluation of Similar Biotherapeutic Products (SBPs), 2009 - to be updated

- EMA quality, non-clinical and clinical guidelines for biosimilars as well as specific guideline on recombinant Interferon-alfa

- USFDA’s series of guidance documents for biosimilars
  - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  - Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

- PMDA’s Guideline for the Quality, Safety and Efficacy Assurance of Follow-on-Biologics (FOBs)

- HC’s Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)
Anticipated requirements - PEG-IFN
Quality part - Module 3

- CTD module 3 for both the active ingredient as well as for the final product, like any other biological product

- In addition, comparability data with appropriate comparator product will need to be submitted
  - comparability in terms of physicochemical properties, stability, biological activity, purity and impurity profile (e.g., the general principles in ICH Q5E could be expanded and used)
    - extensive characterization using battery of state-of-the art validated analytical methodologies including biological activity tests (bioassay)
  - will determine the extent of safety/efficacy data required and whether the proposed product can be considered bio-similar
  - minor differences should be evaluated vis-à-vis their impact on safety/efficacy
  - PQ can identify appropriate comparator product
Anticipated Safety/efficacy requirements - PEG-IFN

CTD Module 4 and 5

- **Non clinical information,**
  - data required depends on the extent of quality data submitted to establish similarity.
  - comparative in vitro studies such as receptor binding studies and bioassays
  - comparative in vivo PD evaluations *(PMDA mentions exemption depending on level of in vitro similarity and other factors)*
  - data from at least one repeated toxicity study in relevant species
  - data on animal immunogenicity
  - local tolerance testing

- **Clinical information**
  - comparative PK analysis in single dose cross over study
  - comparative PD studies using suitable markers
  - comparative clinical efficacy and safety data including clinical immunogenicity assessment, *(PMDA suggests that PK/PD studies could be sufficient in certain cases to demonstrate clinical efficacy)*

- **Risk management (PV) plan/post market surveillance programme**
USFDA’s step-wise and totality of evidence approach

- Manufacturers who have already progressed with much of the development activity may wish to follow totality of available evidence approach to demonstrate comparable quality and safety/efficacy with the reference product.

- Those who are at an early development stage or intend to develop the product may use a step-wise approach such that comparability is adequately established and differences are understood at each stage.
PQ, subject to adequate funding and inclusion of the medicines in EOI, may be able to organize technical assistance to manufacturers to help with GMP issues and dossier compilation.

PQ is always available to respond to specific questions.

PQ can facilitate country registration:
- organization of joint assessments with target countries for simultaneous PQ and country registrations
- use of PQ’s collaborative procedure for fast track registration in countries, following prequalification.
Further information:  http://www.who.int/prequal/

Email:  prequal@who.int