Manufacturers Meeting
Copenhagen – September 2012

Quality Assessment: Updates
Acronyms!

API: active pharmaceutical ingredient
CEP: EDQM certificate of suitability
CTD: common technical document
EC: expert committee
FPP: finished pharmaceutical product
GL: guideline
ICH: International Conference on Harmonization
FDC: fixed-dose combination
FPP: finished pharmaceutical product
Acronyms!

MRA: mutual recognition agreement

PQP: Prequalification of Medicines Programme

QIS: quality information summary (required quality template)

QOS-PD: quality overall summary – product dossier (required quality template)
Overview

- Quality guidelines
  - Key published quality guidelines
  - Newly published quality guidelines
  - Guideline revisions planned or in progress
- Update to the variation guideline
- Updated practices
The challenge

“Where is the knowledge we have lost in information?”

T.S. Eliot

"Knowledge is of two kinds: We know a subject ourselves, or we know where we can find information about it."

Samuel Johnson
WHO PQP Published Guidelines


Comprehensive list available for download at:

PREQUALIFICATION PROGRAMME
A United Nations Programme managed by WHO

Vision
Good quality medicines for everyone.

Mission
In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need.

This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

Strategy
- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Key output
The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Programme is used principally by United Nations agencies including UNAIDS and UNICEF to guide their procurement decisions. But, the list has become a vital tool for any agency or organization involved in bulk purchase of medicines, at the pharmacy level, and international level.
Information and Guidelines

- Expression of Interest (EOI) Lists
  - Invitations for Expression of Interest (EOI)
    - How to submit an EOI

- General information related to prequalification of medicines
  - General procedure [pdf]
  - How to participate in the Prequalification
  - Where to send the Product Dossier, as well as APIMF documentation and Site Master File
  - Dates of Copenhagen assessment sessions
  - Confidentiality
  - Meetings with PQP Assessors
    - Meeting Request Form

- Prequalification guidelines related to medicinal products
  - Prequalification guidelines

- The APIMF procedure
  - General information [pdf]
  - Changes to the details of an accepted APIMF (amendments and updates) [pdf]

- Variations (changes) to prequalified medicines
  - An introduction to the variation procedure
    - TRS943, Annex 6 - guidance on variations to a prequalified product
  - Types of variations
  - How to submit a variation
    - Variation application form
  - Where to submit the variation application
  - Grouping of variations
  - Updated stability requirements for variations
  - Information regarding API-related changes
    - APIMF-related Notification Form
Key published quality guidelines


- Guidance on variations to a prequalified product dossier: TRS 943, Annex 6 (2007)

Key published quality guidelines


- **Stability** testing of APIs and FPPs: TRS 953, Annex 2 (2009)
Recently published related guidelines

- **Procedure for prequalification** of pharmaceutical products: TRS 961 Annex 10 (2011)

- Guidelines on submission of documentation for prequalification of **innovator FPPs approved by SRAs**: TRS 961 Annex 11 (2011)

[SRA: stringent regulatory authority (ICH members, ICH observers, and authorities associated with an ICH member through an MRA)]
Newly published general quality guidelines (1)


Available at:

Detailed information on preparation of the dossier in CTD format:

How to format the dossier

The expected contents of modules including details of module 1 (regional information)
Progress since this publication

Section 5 on Module 3 (quality) describes the three options for submission of API information:

- Use of CEP, use of APIMF, or full data in the dossier.

In the interim, the process for prequalification of APIs has been established. Therefore the newly published quality guideline (described next slides) describes four options for submission of API information:

- Prequalified API, CEP, APIMF, or full data in the dossier.

- The newest option will be addressed in Dr Fake’s presentation

Available at:


Comprehensive Q GL - detailed information on the technical requirements for the dossier to be submitted for quality assessment.

Wherever there is conflict between TRS Annex 4 and other GLs, TRS 970 Annex 4 prevails in PQP.
Example detailed guidance
3.2.S.3.2 Impurities

Which impurities to discuss/investigate

How to use monograph limits

Possible application of GL principles to some semi-synthetic APIs

An additional (to ICH) method for qualifying an impurity level

Revisions planned or in progress

- FDC guideline (current 2005) – may be targeted for revision in the future

- Guidelines on submission of documentation for prequalification of **generic FPPs approved by SRAs**: not yet published (scheduled to go through the EC process in 2013)

- **Variation guidelines** (current 2007)

- Additional guidance for variations to be applied by API manufacturers (no current guidance is available)
Variation Guideline

The variation guideline is intended to:

- assist applicants with the **classification of changes** made to the quality part of a prequalified FPP

- provide guidance on the technical and other general data requirements to **support changes** to the quality attributes of the API or FPP
Variation guideline – revision progress


- Starting March 2011, PQP began drafting a revised variation guideline.

- Several draft stages have been completed, including circulation to PQP applicants for feedback (over 100 recipients) and redrafting with consideration given to the responses.

- The GL has now gone through the first EC circulation and the comments have been collected.
Variation guideline – revision progress

- The draft GL will be presented to the EC meeting in October in Amsterdam.

- Comments received that have a significant effect on the GL will be highlighted and discussed at this meeting.

- Due to the complexity of the GL, it is likely that a further EC meeting circulation will be required.

- Finalization of the GL is targeted to be in 2013.
Variation Guideline Revision: Advantages


- Revised variation GL is aligned with the updated quality GL:
  - Organized in CTD format – easier to find the relevant change
  - Expanded detail – requirements have not significantly changed, however requirements are transparent and more explanatory
  - Requirements aligned e.g. stability (reduced requirements), dissolution profiles
Variation Guideline Revision: Advantages

Some changes will be possible to implement without prior acceptance:

Notifications: notifications do not require prior acceptance, but must be notified to WHO PQP immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

There are about 45 IN and about 60 AN classifications.
Variation Guideline Revision: Advantages

Some major variations (Vmaj) have been reclassified as minor variations (Vmin). These include classifications that were previously Vmaj by default:

- Immediate packaging of API
- Specs/methods for immediate packaging of API
- Quantitative change in composition of FPPs
- Addition or removal of a scoreline

(Listed conditions must be met in order to meet Vmin classification.)
Variation Guideline Revision: Advantages

- Some minor variations (Vmin) have been reclassified as immediate notifications (IN):
  - Change in API site without change in specifications, method of manufacture and route of synthesis
  - Reduction of retest period (not due to unexpected events)
  - Addition or replacement of components of the colouring or flavouring system
Variation Guideline Revision: Advantages

- Some minor variations (Vmin) have been reclassified as annual notifications (AN):
  - Addition of an analytical procedure for control of the API
  - Some changes in manufacturing process of FPP (with listed conditions met)
Updated practices

- In parallel with updated guidelines, there have been significant updated practices in the past 2 years.

- Reduced requirements
  - General
  - For specific therapeutic categories

- Other updates including general application requirements
Updated Practices - General

- **September 2010:** reduced requirements for 1) the number of FPP batches required to establish the shelf-life, and 2) for “established” generic products.

1) The number of FPP batches required to establish the shelf-life has been reduced from 3 pilot to $\geq$ two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate release solid FPPs (with noted exceptions) and non-sterile solutions), at minimum one batch of at least pilot scale, and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules).
Updated Practices

- [A “complicated” FPP includes sterile products, inhalation and transdermal products, and FDCs including ritonavir/lopinavir, rifampicin or an artemisinin.]
2) **Established generics** are those that have been marketed for at least 5 years, and they have manufactured either 10 batches in the past year, or 25 batches in the past 3 years.

Instead of process validation and some pharmaceutical development data, the applicant may provide a product quality review (PQR) (previously known as the "annual report").
Updated Practices

- In summary, for established generics, the PQR replaces the developmental pharmaceutics data in the sections on 1) formulation development (P.2.2.1 a)) and 2) manufacturing process development (P.2.3 a)) of the CTD. In addition, it replaces the section on process validation, P.3.5 of the CTD.
Updated Practices

- **March 2011**: QIS and QOS-PD templates required to be submitted as part of a dossier application
- **September 2011**: CTD format required for the dossier (including QIS and QOS-PD templates)
- **September 2011**: required stability conditions for PQ are 30° C/65% or 30° C/75% for API, 30° C/75% for FPPs.
Updated practices

- **API related updates** – to be covered by Dr. Fake

- **Other significant changes:**
  - Reduced requirements at time of submission for RH products (in line with 2nd-line TB requirements)
  - **Quality templates are updated periodically** – ensure the current versions are downloaded from the website when preparing your dossier

    E.g. current QIS/QOS-PD templates are dated July 2012
Summary

- In order to meet current requirements, be aware of:
  - the current guidelines – found through the PQP website
  - the newly published quality guidelines – these prevail where there is any noted difference compared to previously published guidelines

- Variation guideline actively under revision

- Updated practices (reduced requirements and updated general application requirements)
Thank you