Principles for Prioritizing Dossiers for WHO Medicines Prequalification

SCOPE

This note outlines the basic principles applied by the WHO Prequalification Team: medicines (WHO) for prioritization of product dossier assessments and inspections of related sites within each therapeutic area.

Prioritization becomes essential when resources are limited.

Prioritization occurs at several levels for medicines prequalification:

- when determining which products are to be included in the Invitations to Manufacturers to Submit an Expression of Interest for Product Evaluation (EOIs). This prioritization is carried out by experts outside of WHO
- during screening of dossiers
- during assessment of dossiers.

Products are included in the EOIs based on their inclusion in the WHO treatment guidelines and/or the WHO Model List of Essential Medicines. The EOIs constitute a selection of priority products recommended by WHO and are "priority lists" in their own right.

Dossiers are screened for completeness as soon as they are received. Screening ensures that assessment resources are directed to dossiers that meet minimum data requirements, as opposed to dossiers that are incomplete and therefore not yet ready for full assessment.

1. PRIORITIZATION DURING ASSESSMENT

Products invited for evaluation by WHO (i.e. included in the respective EOI) and accepted for assessment (i.e. have passed screening) are ranked as follows:

Priority 1 - no similar* product in the prequalified list.

Priority 2 - one similar product in the prequalified list

Priority 3 - two similar products in the prequalified list

Priority 4 - three similar products in the prequalified list.

Priority 5 - >three similar products in the prequalified list

** For the purpose of this note only, two products are considered to be similar if they contain the same active pharmaceutical ingredient (API), and are of the same dosage strength and dosage formulation*

Within each priority level (1–5), the highest priority is given to an application from a company with one or more previously prequalified products; previously prequalified products are a measure of a company's ability and readiness to progress a product from submission of the dossier to prequalification of the product.

Specific products are further prioritized based on recommendations made by WHO clinical departments.[1]

[1] With regard to specific product categories in the EOIs, antiretrovirals (ARVs) are usually prioritized over non-ARVs. Also, second-line ARVs are generally prioritized over first-line products. Furthermore, fixed-dose combination products (FDCs) are prioritized over single-ingredient products or co-packaged products, across all therapeutic areas. However, some single-ingredient products — such as generic darunavir, second-line TB products and artemisinin-based rectal and injectable formulations — are in high demand. Paediatric formulations (especially FDCs) or formulations for adults with a paediatric indication (e.g. scored formulations) are a priority across all therapeutic areas, especially dispersible formulations or other types of more child-friendly paediatric formulations (with respect to HIV/AIDS treatment, a strategic move is being made by WHO towards "one pill, once-a-day FDCs", in preference to three-times-a day regimens.)

The priority of a product may change if:

- other products of the same kind become prequalified during assessment
- a product's associated bioequivalence (BE) study is rejected (for example, because the comparator product used is unacceptable) since it will take time for the company to conduct a new BE study and possible reformulation of the product may entail additional assessment of quality data related to the reformulated product
- the timelines for company responses to WHO requests for additional data are excessive in relation to the type and extent of data requested
- the company does not respond to reminders to reply to WHO requests for additional data;
- the quality of the company's response to WHO requests for additional data is poor, i.e. if despite repeated requests the company fails to address the critical dossier issues
- if the company upgrades or downgrades its own prioritization of a product in its product portfolio.

Good manufacturing practice (GMP) and good clinical practice (GCP) status are also taken into account. For instance, a Priority 1 product with outstanding GMP and/or GCP issues could temporarily be assigned a lower priority than a Priority 2 product which meets GMP and GCP requirements. For specific considerations relating to prioritization of inspections, please see below.

2. PRIORITIZATION OF INSPECTIONS

Inspections are generally prioritized based on the known potential or perceived risk of a substandard product to the patient. The higher the risk, the higher the site will be prioritized for inspection. The following factors are considered during risk assessment:

2.1 Product type and activity of the site:

PRODUCT TYPE / ACTIVITY	RISK CATEGORY			
	CRITICAL	HIGH	MEDIUM	LOW
Finished pharmaceutical products (FPPs):				
Sterile finished products	X			
Non-sterile finished products		X		
Active pharmaceutical ingredients (APIs):				
Sterile APIs		X		
Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc.)			X	
Other non-sterile APIs				X
Quality control laboratories (QCLs):			X	
Contract research organizations (CROs):			X	

2.2 All known factors that could influence quality, safety and efficacy, including the following:

2.2.1 Results of previous WHO GMP inspections

2.2.2 Results of inspections by other acceptable regulators (PICS[2]/US Food and Drug Administration (US FDA)/European Directorate for the Quality of Medicines & HealthCare (EDQM))

2.2.3 Recalls or complaints since last inspection

2.2.4 Results of product testing

2.2.5 Significant changes within the manufacturer, e.g. changes to key personnel

2.2.6 Nature of buildings, equipment, products, etc

2.2.7 Specific recommendations from the WHO assessors of the respective dossier

2.2.8 Any other relevant information

2.3 Due date: Routine re-inspections are scheduled within the period three months before or three months after the due date as recommended after the previous inspection.

2.4 API specific risk factors

2.4.1 Polymorphism

2.4.2 Solubility in water

2.4.3 Complexity of the route of synthesis

2.4.4 Solvents used (class and/or recovered solvents)

2.4.5 Impurities (e.g. risk of genotoxic impurities)

2.4.6 Sterile API

2.4.7 Fermentation

2.4.8 Toxicity/activity/potency

2.4.9 Particle size

2.4.10 Other properties to be considered

2.4.11 Site compliance information (WHO/EDQM/USFDA/other)

[2] The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S).

2.5 CRO/bioequivalence-specific risk factors

2.5.1 Formulation, e.g. FDC

2.5.2 Solubility in water

2.5.3 Polymorphism

2.5.4 Biotherapeutics Classification System classification

2.5.5 CRO compliance history (results of previous WHO GCP/GLP inspections)

2.5.6 Specific recommendations from the assessors of the respective dossier

2.6 General considerations

The inspection planning cycle is 6–12 months, which includes any time taken by companies to declare readiness for the inspection. In case of rescheduling an inspection, a minimum of three months' notice is needed.

2.6.1 New sites that have not been inspected before are prioritized

2.6.2 Products and sites associated with higher risk are prioritized

2.6.3 Sites for products with specific recommendations for inspection from PQP assessors are prioritized

2.6.4 Progress of the dossier will be taken into account in order to provide timely information about the compliance of the site or study, to facilitate the decision as to whether the product can be prequalified. Follow-up inspections of sites whose product dossiers are not progressing are not prioritized

2.6.5 The due date for the next inspection is determined at the conclusion of the previous inspection but may be modified based on new information which affects its risk ranking.

3. ADDITIONAL CONSIDERATIONS

A product that is close to prequalification will be prioritized, irrespective of its initial priority level. For instance, if one part of the dossier (quality or bioequivalence) is acceptable and only a few issues remain outstanding for the other part, WHO will progress that dossier to prequalification by requesting the necessary data from the company via e-mail, and by carrying out any assessment immediately upon receipt of the additional data, independent of the bi-monthly assessment sessions.

WHO prioritization may change at any time following revision of WHO treatment guidelines, perceived medical need as reflected in updates of the EOIs, or issues relating to drug safety, for example, as communicated in updates received from WHO clinical departments. However, the assessment of a product that has been accepted for assessment, but which is now no longer invited for evaluation in the current EOI will, in most cases, continue until prequalification. This was the case, for example, for products containing stavudine 40 mg, which were under assessment at the time when (2009) WHO issued recommendations against this stavudine dosage.

WHO prioritization may change if there is a sudden increase in demand for a particular product, or product group. In case of emergency situations (such as outbreak of H1N1 influenza, emergency supply shortages etc.) with potential for substantial damage to public health, re-prioritization amongst priorities may be necessary giving temporarily the highest priority to the product(s) in need.

It is important to note that the assessment part of WHO can usually re-prioritize its assessment of a dossier at very short notice, whereas the WHO Inspection Services have much longer timelines in terms of rescheduling inspections (see details above).