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World health organization's procedure for prequalification of medicinal products

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ABSTRACT

The purpose of this study is to understand the process of prequalification of medicinal products followed by World Health Organization for inclusion of product in WHO Model List of Essential Medicines. WHO undertakes a comprehensive evaluation of the quality of medicinal products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. This is done through a standardized quality assessment procedure which is based on WHO-recommended quality standards.

Key words: Prequalification, WHO Model List of Essential Medicines, Expressions of interest, Product Dossier, Multisource Product.

INTRODUCTION

Prequalification is the standardized quality assessment procedure of WHO to evaluate the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Agencies using information resulting from the prequalification procedure should perform additional steps of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, preshipment quality control and other related aspects.

WHO undertakes a comprehensive evaluation of the quality of medicinal products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. The products found to meet the WHO-recommended quality standards are included in the list of medicinal products, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies. The list of prequalified

medicinal products is principally intended for use by United Nations agencies – including the Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF) and United Nations Population Fund (UNFPA) – to guide their procurement decisions. The growing list of medicinal products that have been found to meet WHO-recommended standards may, however, also be of interest to other organizations, including countries wishing to engage in the bulk procurement of medicinal products [1].

EXPERIMENTAL SECTION

The secondary data used in the study was obtained from various official reports published by World Health Organization and internet. The study is of descriptive type and method used is the description.

Procedure

At regular intervals, in consultations with United Nations agencies, WHO will publish an invitation to interested parties, requesting them to voluntarily participate in this procedure in respect of the products mentioned in the Invitation. By submitting an expression of interest, the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified medicinal products along with changes carried out and/or planned.

Invitation for Expressions of Interest

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the medicinal products listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press. In situations of high public health concern as determined by WHO, the Organization may also directly invite relevant parties to submit specified products for assessment by WHO under this procedure without publication of an invitation for expressions of interest [2].

Data and Information to be submitted

Interested parties are expected to submit documentation on the medicinal products as called for in the invitation for EOI. Applicants should submit their product dossiers with the required information to the WHO focal point, before the deadline specified in the invitation [3].

In submitting an EOI for product evaluation, the applicant should send the WHO focal point the following:

- A covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct;
- A product dossier, in the format specified in the WHO guidance documents for submitting product data and information;
- Product samples, to enable visual examination and chemical and pharmaceutical analysis;
- A site master file for each manufacturing site listed in the product dossier, in the requisite format specified in the WHO guidance documents for submitting a site master file.

The documentation should be submitted in English in the format described by WHO. Electronic submission of documentation is encouraged and should be submitted in the WHO-recommended format together with a covering letter cross-referencing the information, as organized electronically.

Screening of Dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness prior to being evaluated. WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the administrative screening will be retained by WHO for evaluation purposes.

Dossier Assessment

The product information submitted in the dossiers will be evaluated by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of: pharmaceutical development, quality assessment of medicinal products, quality assurance, biopharmaceutics and other relevant fields. The assessors must comply with the confidentiality and conflict of interest rules of WHO. In emergency situations, as determined by WHO, a fast-track assessment procedure, as defined in a specific SOP, shall be used to facilitate the rapid evaluation of priority products. Each applicant may request a hearing or meeting with the WHO experts involved in the assessment of this applicant's dossier to clarify issues identified by the WHO experts. In case of multisource generic products, WHO may provide technical assistance to applicants regarding appropriate product information to be submitted as well as production and control requirements.

Site Inspection

WHO will plan and coordinate the performance of site inspections of the manufacturing site(s) of the API(s) and the finished product, and of the clinical testing units or CROs, as needed to assess compliance with cGMP as recommended by WHO and include data verification. Site master files submitted by the applicant will be reviewed before an inspection is performed. The inspections of clinical testing units or organizations are carried out to assess compliance with cGCP and cGLP, and to perform data verification. The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from DRA inspectorates, who will act as temporary advisers to WHO. A WHO staff member will coordinate the team. Each team will perform the inspections and report on its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative of the DRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with cGMP and cGCP/cGLP [2].

Reporting and Communication of Results of the Evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant, manufacturer(s) and/or testing unit(s) or organization(s), where relevant.

The inspection report will be communicated to the applicant, manufacturer(s) and/or contract research organization(s). If any additional information is required or corrective action has to be taken by the manufacturer(s) or clinical testing unit(s) or organization(s), WHO will postpone its decision of the acceptability of the respective site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate the procedure of quality assessment of a specific product if the applicant is not able to provide the required information or implement the corrective actions in a specified time period, or if the information supplied is inadequate to complete the quality assessment process [4].

In the event of any disagreement between an applicant and WHO, an SOP established by WHO for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially confidential information of the applicant, manufacturer(s) and/or testing organization(s) [5].

Outcome of Quality Assessment Procedure

Once WHO is satisfied that the quality assessment process is complete for the relevant product, and that the WHO-recommended standards are met, the product, as produced at the specified manufacturing site(s), will be included in the list of prequalified medicinal products. The list of prequalified medicines will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list.

Each applicant will receive a letter from WHO informing it of the outcome of the quality assessment process in regard of the submitted product(s). Once the product(s) are included in the list of prequalified medicinal products, the applicant shall be held to keep WHO continuously updated on all relevant aspects of the manufacture and control of such product(s) and to implement the required commitments, as agreed with WHO.

Maintenance of Prequalification Status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have impact on the safety, efficacy and quality of the product, following the WHO *Guidance on variations to a prequalified product dossier*, as adopted in 2006 (7) and its revisions. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant.

WHO will at regular intervals furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the reassessment procedure will also lead to removal from the list.

Re-evaluation, including re-inspections, shall also be performed:

- If any fraud or omissions by the applicant, manufacturer(s) of finished product or API, or clinical testing units or organizations in the initial assessment procedure or during the follow-up activities, becomes evident; and
- If WHO or any United Nations procurement agency considers that a batch or batches of supplied prequalified medicinal products are not in compliance with the specifications which were found to be applicable upon prequalification [6].

RESULTS AND DISCUSSION

The purpose of the quality assessment procedure is to evaluate whether certain pharmaceutical products (considered by WHO to be vital for HIV/AIDS, tuberculosis, malaria and other diseases, or for reproductive health) meet the requirements recommended by WHO and are manufactured in compliance with current WHO good manufacturing practices (cGMP).

WHO may also collaborate with DRAs in the quality assessment. WHO recommends that applicants expressing interest in participation in the prequalification procedure inform the DRA in the country of manufacture of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that applicants provide the DRA with the necessary authorization to discuss the relevant product files with WHO representatives during dossier assessment and site inspections.

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