Annex 4

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products

1. Introduction

A significant part of the quality of a finished pharmaceutical product (FPP) is dependent on the quality of the active pharmaceutical ingredients (APIs) used for its production. Under the World Health Organization (WHO) guidelines on good manufacturing practices (GMP), it is the manufacturer of the FPP who is responsible for the overall quality of the product, i.e. including the choice of the suppliers and manufacturers of the ingredients.

However, in the context of globalization, APIs are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high. A proper system of qualification of suppliers can promote the constant sourcing of active ingredients of appropriate quality and thereby safeguard public health interests.

Full evaluation of suppliers of APIs, however, is a cost-intensive and resource-demanding activity, which only a few national medicines regulatory authorities (NMRAs) can afford. As a result, API assessment is not often part of granting marketing authorizations to FPPs, a situation which can undermine the quality and safety of marketed pharmaceutical products.

The need for quality assurance of APIs was noted in the resolutions of the 12th International Conference of Drug Regulatory Authorities in 2006. If adopted and implemented, this procedure would assist procurement agencies in validating the quality of the pharmaceutical products they are purchasing and facilitate product evaluation by NMRAs of WHO Member States as part of the marketing authorization procedures.

The purpose of this procedure is to provide relevant United Nations agencies and relevant authorities of WHO Member States, such as NMRAs, with advice on the acceptability, in principle, of APIs which are found to meet WHO-recommended quality standards.

Those APIs and their specified manufacturing sites which are found to meet the quality standards recommended by WHO are included in a list of APIs, as manufactured at the specified manufacturing sites, which have – at the time of their evaluation and inspection by WHO – been found to be acceptable, in
principle, for use in the production of pharmaceutical products. It remains
the ultimate responsibility of the manufacturer of the FPP to ensure that the
API, as accepted in principle, is suitable for the manufacture of the specific
pharmaceutical product, for example in a sterile or a fixed-dose combination
product.

Inclusion in the list does not imply any approval by WHO of the APIs
and manufacturing sites in question. Moreover, inclusion in the list does
not constitute a WHO endorsement or warranty of the fitness of any API
for a particular purpose, including its use in a particular pharmaceutical
product and the safety and/or efficacy of that pharmaceutical product in the
treatment of specific diseases.

2. **Glossary**

The definitions given below apply to the terms used in this procedure. They
may have different meanings in other contexts.

*active pharmaceutical ingredient (API)*

Any substance or combination of substances used in a finished product,
intended to furnish pharmacological activity or to otherwise have direct
effect in the diagnosis, cure, mitigation, treatment or prevention of disease,
or to have direct effect in restoring, correcting or modifying physiological
functions in human beings.

*finished pharmaceutical product (FPP)*

A finished dosage form of a pharmaceutical product that has undergone
all stages of manufacture, including packaging in its final container and
labelling.

*manufacture or production*

All operations of purchase of materials and starting materials, preparation
of the API and of the pharmaceutical product, including packaging and
repackaging, labelling and re-labelling, quality control, release, storage
and distribution and the related controls. The terms “manufacture” and
“production” are used interchangeably in this document.

*manufacturer of active pharmaceutical ingredient (API)*

A company that produces, packages and labels active pharmaceutical
ingredients (APIs).

3. **Purpose and principles**

The purpose of this quality assessment procedure is to evaluate whether the
APIs meet the requirements recommended by WHO, including that they
are manufactured in compliance with WHO current good manufacturing practices (current good manufacturing practices being hereinafter referred to as GMP) \((I, 2)\). This will be done through standardized quality assessment and inspection procedures.

The quality assessment procedure established by WHO is based on the following principles:

- a general understanding of the production and quality control activities of the manufacturer of the API;
- assessment of data and information on the API, submitted by the manufacturer, which includes the manufacturing process, material specifications, test data and results, including changes and variations;
- assessment of the API manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key starting materials or intermediates and the final APIs during and after purification through compliance with WHO GMP;
- random sampling and testing of APIs;
- control of storage and distribution;
- handling of complaints and recalls; and
- monitoring of complaints from relevant United Nations agencies and national medicines regulatory authorities of WHO Member States.

WHO will collaborate with NMRAs and other organizations on quality assessment and site inspections. WHO recommends that manufacturers of APIs expressing interest in participating in the prequalification of APIs should inform and ask the relevant NMRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the national medicines regulatory authority with the necessary authorization to discuss the product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

4. **Steps of the procedure**

WHO undertakes a comprehensive evaluation of the quality of APIs, based on information submitted by the applicants, and inspection of the relevant manufacturing site(s).

At regular intervals WHO will publish an invitation to interested parties, asking them to voluntarily participate in this procedure in respect of the substances mentioned in the invitation. By submitting an expression of interest (EOI), the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified APIs together with any changes carried out and/or planned.
Interested applicants provide the necessary information to WHO by submitting an API dossier and other information as requested. Assessment will normally include evaluation of:

- API dossiers, which must include data and information as specified in the guidelines for submission (the guidelines are available on the WHO website (www.who.int/prequal)); and
- manufacturing sites of APIs, which must adhere to WHO GMP.

If evaluation demonstrates that an API and its corresponding manufacturing site(s) meet the standards recommended by WHO, it will be included in the list of APIs which have – at the time of their assessment and inspection – been found to be acceptable, in principle, for use in production of pharmaceutical products.

WHO reserves the right to terminate the procedure of quality assessment of a specific API if the applicant is not able to provide the required information, and/or the applicant is unable to implement any corrective actions, which WHO may require, within a specified time period, or when the information supplied is inadequate to complete the quality assessment process.

WHO recognizes the evaluation of relevant APIs by competent authorities which apply stringent standards for quality, similar to those recommended by WHO, such as, for example, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMEA), and the European Directorate for the Quality of Medicines & HealthCare (EDQM).

Provided that the competent authority applying stringent standards is willing to share certain information with WHO on the API in question, WHO will consider this information for possible inclusion of the API in the list of WHO prequalified APIs. It will do so as and when information about such APIs becomes available to WHO. These products can be added to the list of APIs prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the competent authority concerned, and the exchange of relevant information between the concerned authority and WHO.

5. **Invitation for expression of interest**

WHO will, at regular intervals, publish an invitation to manufacturers of specific APIs as identified in the invitation to submit an API dossier for evaluation in accordance with this procedure and the relevant guidelines.

The APIs listed in an invitation for expressions of interest (EOI) will generally be APIs for pharmaceutical products which:
— are considered by WHO to be vital for the effective treatment and prevention of the specified diseases, for example, but not limited to, the treatment of HIV/AIDS, malaria or tuberculosis; and which
— the WHO Expert Committee on Specifications for Pharmaceutical Preparations has identified as being of highest concern in relation to quality.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the APIs listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

Guidelines developed for the submission of the API dossier are available on the WHO web site at www.who.int/prequal and will be sent to interested manufacturers upon request.

6. Data and information to be submitted

Interested manufacturers are expected to submit documentation on the APIs as called for in the invitation for EOI. Applicants should submit their API dossiers, with the required information, to the WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers shall be made available on the WHO web site. Data and information to be submitted in the API dossier should include the following:

**General information**
- nomenclature
- structure
- general properties

**Manufacture**
- site(s) of manufacture
- description of manufacturing process and process controls
- control of materials
- control of critical steps and intermediates
- process validation and/or evaluation
- manufacturing process development

**Characterization**
- elucidation of structure and other characteristics
- impurities

**Control of the API**
- specification
• analytical procedures
• validation of analytical procedures
• batch analysis
• justification of specification

Reference standards or materials

Container closure system

Stability
• stability summary and conclusion
• post-approval stability protocol and stability commitment
• stability data.

The above-listed content of the API dossier is the same as the common technical documentation (CTD) content for the API section and is in line with the content of the API master file (APIMF) dossier, open and restricted parts together, as established for the purposes of WHO prequalification of pharmaceutical products (3).

Holders of APIMFs whose dossiers as per the CTD have been assessed with a positive notified outcome by WHO as part of the prequalification procedure for a pharmaceutical product, and whose product has subsequently been included in the list of WHO prequalified pharmaceutical products can, in response to an invitation for EOI, apply in writing for evaluation under this API prequalification procedure without dossier assessment. WHO, however, reserves the right to assess those issues which are required to be evaluated under the present procedure, but which were not covered by the assessment of the APIMF dossier as part of the prequalification of a pharmaceutical product.

Alternatively, a drug master file, as prepared for or submitted to the NMRA of an ICH\(^1\) region, can be submitted provided that it contains the information required. In such cases a covering letter cross-referencing the information should be provided by the manufacturer. In this regard, the WHO Pharmaceutical Starting Materials Certification Scheme (SMACS) can be used in support of the relevant data which are covered by the Scheme (4).

Changes in the manufacture of an API should be documented in the API dossier through appropriate change control procedures and communicated to WHO.

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\(^1\) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
7. **Screening of dossiers submitted**

Each API dossier submitted by an applicant will be screened for completeness prior to being evaluated. Dossiers submitted for APIs, which are not listed in an invitation for EOI or which have not otherwise been invited by WHO, will not be accepted for evaluation.

Similarly, 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.

8. **Assessment of API dossiers**

The information on the API submitted in the dossier 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 pharmacy, organic and analytical chemistry, quality assessment, quality assurance and other relevant fields.

The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NMRAs and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

9. **Site inspection**

Dependent on the outcome of the evaluation of the API dossier, the planning of inspections should take into account the types of API and the results and reports of inspections conducted by regulatory authorities or other competent organizations.

WHO will plan and coordinate the performance of inspections at the manufacturing site(s) of APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of WHO GMP guidelines, and will compare the technical information on the manufacturing process
given in the API dossier submitted to WHO with the manufacturing process actually carried out on site.

The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from NMRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in WHO GMP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

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 NMRA of the country of manufacture would normally be expected to accompany the team to the manufacturing facilities to assess the compliance with GMP.

10. 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.

The findings from the dossier assessment, including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant and will request submission of the missing data and information and for corrective actions, as appropriate.

The inspection report will be communicated to the applicant. If any additional information is required, or corrective action has to be taken by the manufacturer of the API and/or manufacturer of the key intermediate, 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 API if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

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 sensitive confidential information of the manufacturer. “Confidential information” means:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. programmes, manufacturing processes or information contained or embodied in an API dossier, unpublished aspects of trademarks, and patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in an exchange of letters between WHO and each applicant, to be concluded before the assessment of the API dossier or inspection of the manufacturing sites.

Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and United Nations agencies.

11. **Outcome of quality assessment procedure**

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

- API application WHO reference number;
- International Nonproprietary Name (INN) of active ingredient;
- name of API manufacturer, physical address of manufacturing site(s);
- applicant reference to pharmacopoeial or in-house standards;
- primary and secondary packaging material(s);
- retest period;
- storage conditions stated on labelling.

Each applicant will receive a letter from WHO informing it of the outcome of the quality assessment process regarding the submitted API applications. Once the APIs are included in the list of prequalified APIs, the applicant shall be held to keep WHO continuously updated on all relevant aspects of the manufacture and control of such APIs and to meet any requirements, as agreed with WHO.
In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will, subject always to the protection of commercially sensitive confidential information, publish WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. WHO shall also be entitled to publish negative evaluation outcomes.

The decision to list an API is made based upon information available to WHO at that time, i.e. information in the submitted API dossier, and on the status of GMP at the facilities used in the manufacture and control of the API at the time of the site inspection(s) conducted by WHO.

This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified API, WHO may delist the API or suspend the API until results of further investigations become available and are evaluated by WHO.

12. **Procurement, sourcing and supply**

All APIs included in the list should hold a certificate granted pursuant to the WHO SMACS prior to moving in international commerce (4).

Procuring United Nations agencies should be aware that manufacturers purchasing APIs from the sources included in the WHO list should still perform the relevant qualification of the manufacturer and quality control of the API with regard to the physicochemical characteristics and other aspects of the API that have an impact on the quality, safety and efficacy of the FPP (5).

Manufacturers of APIs, in turn, should be aware that inclusion in the list does not exclude their duties to communicate to buyers the necessary technical data.

13. **Maintenance of prequalification status**

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the API. It is the applicant’s responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the quality of the API that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant.
Adherence to the reporting requirements will be verified during the inspections carried out by WHO.

Random samples of APIs supplied to manufacturers of FPPs may be taken by WHO or by the NMRA of a Member State and submitted to WHO for independent testing. Certificates of analysis released by the manufacturer and specifications for test methods should be provided by the manufacturer to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate this to the manufacturer concerned.

Complaints concerning prequalified APIs, communicated to WHO, will be investigated in accordance with an SOP established by WHO for that purpose. After investigation WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant, and to the NMRA of the country where the manufacturing site is located. Subject always to considerations of commercially sensitive information as referred to above, WHO also reserves the right to make such reports public if it considers this to be of public health concern. In addition, WHO reserves the right to share the full report with relevant authorities of interested Member States of the Organization and United Nations agencies.

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

Re-evaluation, including reinspections of manufacturing sites, will be done at regular intervals based on risk assessment, but at least once every five years.

Re-evaluation, including reinspections, shall also be performed:

- if any fraud or omissions by the applicant/manufacturer of APIs in the initial assessment procedure or during the follow-up activities becomes evident; and
- if WHO or any of the relevant United Nations agencies or NMRA's of WHO Member States consider that a batch or batches of prequalified APIs supplied are not in compliance with the specifications which were found to be applicable upon prequalification.

14. **Cost recovery**

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.
15. **Confidentiality undertaking**

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned activities, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

16. **Conflict of interest**

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree, that at the manufacturer’s request, WHO will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO,
the manufacturer may object to a team member’s participation in the site visit. Such an objection must be made known to WHO by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

References


