PROCEDURE FOR ASSESSING THE ACCEPTABILITY, IN PRINCIPLE, OF ACTIVE PHARMACEUTICAL INGREDIENTS FOR USE IN PHARMACEUTICAL PRODUCTS

The WHO Expert Committee on Specifications for Pharmaceutical Preparations has been informed periodically of the development of the WHO Prequalification Programme for Priority Essential Medicines. Since its creation the Programme has been responsible for the publication and update of lists of prequalified pharmaceutical products and manufacturers, complying with international standards of quality, safety and efficacy.

In line with discussions held during the 40th and 41st meetings of the above WHO Expert Committee and the April 2006 ICDRA regarding the need for a Prequalification Programme for Active Pharmaceutical Ingredients (API) this new procedure has been drafted for possible adoption following the usual consultation process. It includes the proposal to publish a list of prequalified APIs and corresponding manufacturers that will also meet international standards. This list, established by means of assessment inspections and controls, is intended to be employed by manufacturers of finished products in order to help them use reliable sources of quality ingredients for pharmaceutical production in the priority areas identified by WHO. The WHO pharmaceutical starting materials certification scheme (SMACS) has been included as one of the tools that can be used, e.g. by manufacturers of finished products, when evaluating the quality of APIs.

Please send any comments you may have on this procedure to Dr Raul Kiivet, Manager, Prequalification Programme: kiivetr@who.int or fax: (41-22) 791 4730 by 30 November 2007. In the meantime this procedure will be discussed during the next meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.
**SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/07.202: PROCEDURE FOR ASSESSING THE ACCEPTABILITY, IN PRINCIPLE, OF ACTIVE PHARMACEUTICAL INGREDIENTS FOR USE IN PHARMACEUTICAL PRODUCTS**

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<td>October 2005 - October 2006</td>
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[Note from WHO Secretariat: headings will be adjusted in accordance with the final draft text and to be consistent with the other prequalification procedures.]

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GLOSSARY

Active Pharmaceutical Ingredient (API)
**Manufacture**


**Manufacturer**


**Pharmaceutical Product**


**Production**

1. INTRODUCTION

A significant part of the quality of the finished pharmaceutical product is dependent on the quality of the active pharmaceutical ingredients (APIs) used for its formulation.

Under current WHO GMP guidelines, it is the manufacturer of the pharmaceutical product who is responsible for the overall operations having an impact on the quality of the medicines, i.e. including the choice of the suppliers and manufacturers of the ingredients.

Pharmaceutical manufacturers have to qualify their suppliers of active ingredients as part of their overall quality systems. However, in the context of globalization APIs are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high.

That is why only a proper system of qualification of suppliers can ensure a constant sourcing of active ingredient of appropriate quality and will safeguard the public health interests.

This, however, is a cost- and resource-demanding activity, which only a few manufacturers can afford and take in hand.

WHO would provide advice to United Nations agencies on the acceptability, in principle, of APIs which are found to meet WHO-recommended quality standards in order to be used in the production of pharmaceutical products. This would be done through standardized quality assessment and inspection procedures.

The purpose of the quality assessment procedure is to evaluate whether the APIs meet the requirements recommended by WHO and are manufactured in compliance with Good Manufacturing Practices (GMP) (2).

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;
- assessment of active pharmaceutical ingredient data and information, including changes and variations, submitted by the manufacturer including the manufacturing process, material specifications and test data and results;
- assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and active pharmaceutical ingredients during and after purification through compliance with GMP;
- random sampling and testing of active pharmaceutical ingredients;
- handling of complaints and recalls; and
- monitoring of complaints from agencies and countries.

WHO would collaborate with drug regulatory authorities (DRAs) and other organizations in quality assessment and site inspections. WHO recommends that manufacturers expressing interest to participate in the prequalification of APIs should inform the relevant DRAs of their
intention and request the DRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the DRA with the necessary authorization in order to discuss the product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

WHO would advise United Nations agencies of the manufacturers whose products have been found acceptable in principle for use in pharmaceutical products through a procedure of quality assessment based on WHO-recommended guidelines and standards, notably through implementation of the WHO pharmaceutical starting materials certification scheme (SMACS).

2. STEPS OF THE PROCEDURE

WHO requires information related to the production and control of active pharmaceutical ingredients and the manufacturing site of active pharmaceutical ingredients. Interested manufacturers should provide this information by submitting an Active Pharmaceutical Ingredient dossier: API dossier. In addition to the evaluation of the active pharmaceutical ingredient information submitted, inspection(s) of the manufacturing site may be performed by WHO or by other equivalent organizations, or in collaboration with them during joint inspections as appropriate. WHO reserves the right to terminate the quality assessment procedure of a manufacturer when the manufacturer is either unable or fails to provide the required information in a specified time period, or when inadequate information is supplied to allow completion of the quality assessment effectively.

2.1 Publication of Invitation for Expression of Interest (EOI)

WHO will, at regular intervals, publish an invitation to manufacturers of specific active pharmaceutical ingredients as identified in the invitation to submit an API dossier for evaluation in accordance with this Procedure. Such an invitation will be published widely, i.e. on the WHO web site and possibly also through other media, such as the international press. The invitation should be open and transparent, inviting all manufacturers to submit an EOI for the product listed in the invitation.

Guidelines developed for the submission of the API dossier shall be available on the WHO web site and will be sent to interested manufacturers upon request.

The types of active pharmaceutical ingredients included will be identified by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, in line with the groups of finished products of highest concern in relation to quality.

2.2 Submission of dossier of prequalification of active pharmaceutical ingredients

Each interested manufacturer should provide the focal point indicated in the EOI, with the API dossier containing the required information before the specified date as determined by WHO.

The information should be submitted in a format reflecting the information summarized below. Alternatively, a standard dossier, as prepared for or submitted to the DRA 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.

Data and information to be submitted in the API dossier should include the following:

- General information
  - Nomenclature
  - Structure
  - General properties

- Manufacture
  - Manufacturer(s)/site 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 content of the API dossier is equivalent to the CTD (Common Technical Documentation) content of API section and the content of APIMF dossier, open and restricted parts both together, already in place within the Prequalification programme of essential priority medicines, finished products. (See Reference 11: Guideline on Active pharmaceutical ingredient master file (APIMF) procedure).

The attention of manufacturers of APIs is drawn that the API dossier submitted within the framework of the present Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products are considered as stand-alone
dossiers. These dossiers will be assessed as independent dossiers while APIMFs are assessed in support of and in relation to a FPP.

Changes and updates to the content of API dossier should be handled by means of appropriate variation procedures in place.

The manufacturers of APIs and corresponding holders of APIMFs whose dossiers have been assessed with a positive outcome can apply in official writing to be directly listed as prequalified, without further assessment, within the framework of this new procedure.

In order to avoid any unnecessary duplication of inspection or assessment and also to improve the collaboration between agencies and organization sharing the same responsibilities, the results of any comparable certification scheme or assessment mechanism as, e.g. WHO pharmaceutical starting materials certification scheme (SMACS), based on evaluation of data equivalent to the content of the dossier described above can be accepted without a further assessment or inspections as relevant.

In addition the comparable scheme or mechanism should be capable of communication to its users the information on site of manufacture, specifications (pharmacopoeial or in-house including analytical methods and complete specifications for impurities (where applicable) and retest period of the API.

The system should also be capable of handling variations. In this case valid and authentic evidence of such regulatory positive assessment and acceptance should be submitted in order that the API be included in the positive list of prequalified APIs.

2.3 Screening of submitted API dossier
Each API dossier submitted by the manufacturer will be screened for completeness prior to its evaluation.

API dossiers that are incomplete will not be considered for evaluation. The manufacturer will be informed that an incomplete dossier has been received, and will be requested to complete the API dossier within a specified time period. In the event of non-compliance the API dossier will, in principle, be rejected on the grounds of incompleteness and will be returned to the manufacturer.

API dossiers that are in compliance with WHO requirements will be retained for evaluation purposes. If warranted, based on the outcome of the evaluation of the API dossier and a formal risk assessment, a site inspection will be considered for:
(a) the manufacturing site(s) of the active pharmaceutical ingredient,
(b) the manufacturing site(s) of key intermediate of the API.

2.4 Assessment of API dossier
The API dossiers will be evaluated by a team of experts appointed by WHO. Evaluators, mainly from DRAs where possible, will be appointed in accordance with a Standard Operating
Procedure (SOP) established by WHO for appointment of evaluators of API dossier. The evaluation will be done in accordance with an SOP established by WHO for assessing API dossiers based on the WHO guidelines to ensure uniformity in evaluation.

Evaluators must have the relevant qualifications and experience.

2.5 Site inspection

Dependent on the outcome of the evaluation of the API dossier, and based on a risk-based approach in selection of inspections taking into account the outcome, results and reports of inspections conducted by other equivalent organizations or regulatory authorities, WHO will plan and coordinate performance of inspections at the manufacturing site(s) to assess compliance with the relevant sections of WHO GMP Guidelines (Annexes 1 to 9) or equivalent (Annex 10) and will compare the technical information on the manufacturing process given in the API dossier submitted to WHO, or in the certification dossier when relevant, with the manufacturing process actually carried out on the site. The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from DRA inspectorates. The inspectors will have expertise in areas such as production and quality control, and will have appropriate experience in GMP of active pharmaceutical ingredients.

A WHO staff member will coordinate the team and the team members will act on a temporary basis as expert advisers to WHO. The team(s) will perform the inspections and report on the findings in accordance with SOPs established by WHO for planning and performing site inspections to ensure a standard harmonized approach.

A representative(s) of the DRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facility to assess the compliance with GMP.

In addition, inspectors of DRAs of developing countries may be invited to participate in the inspection as observers for capacity building purposes.

2.6 Report and outcome of evaluation

The evaluators and inspection team(s) will finalize reports according to the established WHO format, describing the findings and including recommendations to the manufacturers. This will be communicated to the manufacturers.

If any additional information is required or corrective action has to be taken by the manufacturer(s) WHO will postpone its final recommendations until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

In the event of any disagreement between a manufacturer 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 and inspection the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the manufacturer contained in this report).

2.7 Assessment result

Once WHO is satisfied that the quality assessment and inspection process is complete for the manufacturer of the pharmaceutical active pharmaceutical ingredient, and that the active pharmaceutical ingredient is acceptable, in principle, to be used in the formulation of a pharmaceutical product (i.e. it has been found to meet the WHO-recommended standards), the active pharmaceutical ingredient, as produced at the specified manufacturing site, will be included in the list.

Manufacturers on the list will be considered as manufacturing the relevant listed active pharmaceutical ingredients of acceptable quality, in compliance with WHO GMP guidelines, with other recommended standards and with the specifications presented in the API dossier, and assessed as acceptable. The quality assessment is valid only for those active pharmaceutical ingredients submitted by the manufacturer in the EOI, evaluated by WHO, and appearing on the list.

Each manufacturer receives a letter from WHO informing the manufacturer of the outcome of the quality assessment process in regard of the particular active pharmaceutical ingredient(s) of that particular manufacturer. A copy of this letter will be sent to the DRA of the country of manufacture.

This list will be compiled in accordance with an SOP established by WHO for final decision-making for inclusion in the list.

The list may include active pharmaceutical ingredients of which the quality and GMP compliance have been assessed and inspected in accordance with other equivalent procedures, including but not restricted to the WHO pharmaceutical starting materials certification scheme (SMACS).

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will publish WHO Public Assessment Reports (WHOPAR(s)) of the active pharmaceutical ingredients, and WHO Public Inspection Reports (WHOPIR(s)) of the manufacturers that were considered to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site.

Results of negative inspections can also be shared with national and regional DRAs.

2.8 Procurement, sourcing and supply

All active pharmaceutical ingredients published on the list should hold a certificate granted within the WHO pharmaceutical starting materials certification scheme (SMACS) prior to moving in international commerce.
The manufacturers of medicinal products should be aware that purchasing their active pharmaceutical ingredient from the listed sources does not exclude their responsibility to perform the relevant qualification of the supplier and quality control of the product according to WHO good manufacturing principle with regard to the physicochemical characteristics and other aspects of the active pharmaceutical ingredient having an impact on the quality, safety and efficacy of the final medicinal product. The manufacturers of APIs, in turn, should be aware that being listed does not exclude their duties to communicate to their pharmaceutical client the necessary technical data.

2.9 Re-evaluation

Re-qualification should be done at regular intervals. Manufacturers and suppliers will be required to communicate changes to WHO that may have an impact on the safety or quality of the active pharmaceutical ingredients.

(i) Re-evaluation of API dossiers will be done as required, should any change regarding the manufacturing method or manufacturing site or any other variation be implemented by the manufacturer, as defined in the relevant WHO SOP. In the absence of any changes, the API dossier should be re-evaluated every 5 years.

(ii) Re-assessment inspections of manufacturing sites will be done at regular intervals, as required based on risk assessment every 1-3 years, but at least once every 5 years.

Manufacturers or products found after re-evaluation incidents or complaints to no longer meet the requirements laid down in the present procedure will be withdrawn from the list. The list will be published and will be included on the WHO web page.

Re-evaluation may also be done in any situation as necessary, including the following:

- If any omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements, including compliance with GMP, as recommended by WHO.

- If any batch or batches of supplied active pharmaceutical ingredients are considered by WHO or other parties not to be in compliance with the agreed specification of the active pharmaceutical ingredient.

- If a complaint considered to be serious in nature has been received by WHO or by other organizations.

- If the certificate of suitability (CEP), or an active pharmaceutical ingredient for which a CEP dossier was submitted, is cancelled or refused based on the assessment of the dossier or for any other reason.

- If, in the opinion of WHO, changes made in the sourcing of key intermediates, route of synthesis, facility or other production, require that a reassessment be made.
2.10 Testing of samples
Random samples of active pharmaceutical ingredients supplied by listed manufacturers or suppliers, will be taken for independent testing of active pharmaceutical ingredients characteristics. Certificates of Analysis of active pharmaceutical ingredients 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 re-evaluation and testing, WHO will investigate the problem and communicate this to the manufacturer.

2.11 Monitoring of complaint(s)
Complaint(s) concerning an active pharmaceutical ingredient or batch of active pharmaceutical ingredients supplied by the manufacturer and communicated to WHO will be investigated in accordance with an SOP established by WHO.

After investigation WHO will provide a written report of the problem and include recommendations for action where relevant.

A copy of the report will be sent to the DRA of the country where the manufacturing site is located. The DRA could be invited to participate in the investigation of the complaint.

WHO will make a copy of the report available to the manufacturer.

2.12 Cost recovery
WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

2.13 Confidentiality undertaking
The evaluators 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 procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached Provisions for evaluators of API dossiers and inspectors (team members participating in site visits) within the scope of the quality assessment procedure of active pharmaceutical ingredients.

A confidentiality agreement should be signed between WHO and any other entities participating in the procedure in order to allow the sharing of information and the preparation of common inspection programmes.

Evaluators and inspectors will take all reasonable measures to ensure that:

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

Evaluators 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.

2.14 Conflict of interest

Before undertaking the work each evaluator and inspector will also be required to sign a Declaration of Interest (in addition to the above-mentioned confidentiality undertaking). If, based on this Declaration of Interest, it is felt that there is no risk of a real or perceived 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 evaluator and inspector is required to confirm that the information disclosed by him/her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to him/her, including that he/she has no financial or other interest in, and/or relationship with a party, which:

(a) may have a vested commercial interest in obtaining access to any confidential information disclosed to him/her in the course of the evaluation/inspection activities described in this document; and/or

(b) may have a vested interest in the outcome of the evaluation activities/inspection including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Each evaluator and inspector will undertake to promptly advise WHO of any change in the above circumstance, including if an issue arises during the course of his/her work of WHO.

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 to WHO regarding any of the inspectors 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 its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.
ANNEX

World Health Organization
Organisation Mondiale de la Santé

PROVISIONS FOR EVALUATORS OF ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILES AND FOR INSPECTORS (TEAM MEMBER PARTICIPATING IN SITE VISITS) WITHIN THE SCOPE OF THE QUALITY ASSESSMENT PROCEDURE OF ACTIVE PHARMACEUTICAL INGREDIENTS

In the course of discharging your functions as an expert adviser to WHO under the attached Agreement for Performance of Work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the active pharmaceutical ingredient(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection you agree:

(a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and

(b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

(i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s); or

(ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the manufacturer(s); or

(iii) becomes part of the public domain through no fault of your own; or

(iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.
You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to you, including that you have no financial or other interest in, and/or other relationship with, a party, which:

(i)  may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii)  may have a vested interest in the outcome of the evaluation of the product(s), in which you will participate (such as the manufacturers of those products or of competing products).

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed___________________________________________

Name (typewritten) ________________________________

Institute _________________________________________

Place ____________________  Date ___________________

Genlproc01
REFERENCES


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