PROCEDURE FOR THE ELABORATION, REVISION AND
OMISSION OF MONOGRAPHS AND OTHER TEXTS FOR
THE INTERNATIONAL PHARMACOPOEIA

Draft revision for The International Pharmacopoeia
(June 2019)

DRAFT FOR COMMENTS

Please send any comments you may have on the attached text to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (schmidt@who.int) by 20 August 2019.

Medicines Quality Assurance working documents will only be sent out electronically and will also be placed on the Medicines website for comment under “Current projects”. If you have not already received our draft working documents, please send your email address to joness@who.int and we will add your name to our electronic mailing list.

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Please send any request for permission to:

Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Regulation of Medicines and other Health Technologies, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland, fax: (41 22) 791 4856, email: kopp@who.int.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/17.767:

Draft revision for *The International Pharmacopoeia*

PROCEDURE FOR THE ELABORATION,

REVISION AND OMISSION OF MONOGRAPHS AND

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[Note from the Secretariat. The International Pharmacopoeia constantly develops new monographs and other texts and revises existing ones to stay abreast of advances in analytical science and regulatory matters. The following text describes the life cycle of compendial texts: how they are developed, revised and, if appropriate, finally omitted from the compendium. The text also covers steps related to the establishment of the International Chemical Reference Substances referred to in analytical tests.]
Procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia

Introduction

Monographs in The International Pharmacopoeia are essential standards to ensure the quality of medicines, thus contributing to their safe and efficacious use. They are developed and maintained in an open and transparent process, in line with the principles outlined in the Good Pharmacopoeial Practices (GPhP)\(^1\) and aimed to foster harmonization and convergence of compendial quality standards to ultimately increase access to affordable, quality-assured medicines.

The following procedure describes the life cycle of texts in The International Pharmacopoeia: how they are developed, revised and, if appropriate, finally omitted from the compendium. The text also covers steps related to the establishment of the International Chemical Reference Substances (ICRS) referred to in analytical tests.

Elaboration of monographs\(^2\)

The steps of the development procedure are as follows\(^3,4\):

Step 1: Identify medicines for which pharmacopoeial monographs need to be developed or revised. Set up a biannual work plan prioritizing medicines that are included in the WHO Model List of Essential Medicines (or are otherwise relevant for WHO health programmes), preferably not already described in pharmacopoeias. Determine whether or not monographs for the corresponding active pharmaceutical ingredients also need to be developed or revised. Confirm the work plan with all WHO parties.

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\(^{2}\) It is intended to add a section on the revision of monographs at a later stage.

\(^{3}\) The procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia was developed by the Secretariat of The International Pharmacopoeia in consultation with the partners involved: Expert, WHO Collaborating Centre, collaborating laboratories and the WHO custodian organization for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines & HealthCare. The steps are therefore described from the perspective of all partners involved.

\(^{4}\) The steps are listed in their chronological order. However, certain steps may overlap during the development of monographs and other compendial texts.
concerned, including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification Team – Medicines.

**Step 2:** Share the work plan with other pharmacopoeias and identify ways of collaboration to reduce the workload of the monograph development and to promote converged or harmonized quality standards that are globally applicable and recognized.

**Step 3:** Contact manufacturers of WHO prequalified medicines and/or of medicines authorized by WHO listed national regulatory systems with an appropriate maturity level\(^5\) to request quality control (QC) specifications and samples of their products.

**Step 4:** Search for relevant information on the product in the public domain, including other pharmacopoeias.

**Step 5:** Assign WHO Collaborating Centres, collaborating laboratories and/or specific experts, if appropriate, to participate in the establishment or revision of the monograph.

**Step 6:** Set up a first version of the monograph based on the available information and on discussions with the partners involved. Perform laboratory investigations to develop, adapt, optimize, verify or validate the proposed analytical procedures. Verify the suitability of the proposed specifications by analyzing medicines from different regions or markets of the world. Identify which of the required reference substances would need to be newly established or are already available either as ICRS or as reference substances established by another pharmacopoeia. In case reference is made to already established ICRS or reference substances established by other pharmacopoeia include these reference substances in the laboratory investigations and advise on their suitability for the new intended use(s). Issue a laboratory report describing the tests performed and the results obtained. Based on mutual agreements, share the laboratory report with other pharmacopoeias with a view to foster harmonization and convergence of compendial quality standards.

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\(^5\) It is intended to refer in the final version of the document to the WHO Global Benchmarking Tool, which is currently under discussion.
Step 7: Follow the consultative process of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP). Circulate the draft text for comments and provide the document on the website of The International Pharmacopoeia.

Step 8: Collate the comments received during the public consultation and review them with the partners involved. If necessary, arrange with the laboratories involved additional laboratory investigations.

Step 9: Discuss the comments received and, if applicable, the results of the additional investigations at an informal consultation with experts. Revise the draft text based on the discussions, as appropriate.

Step 10: Repeat steps 7 to 10 until the text is deemed suitable for adoption.

Step 11: Identify and contact manufacturers (or other potential donors of candidate materials) to ascertain the availability of candidate materials for the establishment of the ICRSs described in the text. Discuss with the WHO custodian organization for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the strategy to establish the proposed ICRSs and its impact on the analytical provisions of the monograph.

Step 12: Submit the draft monograph (together with the laboratory report and a compilation of the comments received during the public consultation) to the ECSPP for information, discussion and/or possible adoption, depending on the maturity of the monograph. If the text is adopted, proceed with step 13. If not, repeat steps 7 to 11.

Step 13: Incorporate all changes agreed during the final discussions leading to adoption, together with any editorial changes.

Step 14: Confirm the final text with the experts and laboratories involved in the final discussions and publish the adopted monograph in a new edition or supplement of The International Pharmacopoeia.

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6 Subject to the availability of the necessary resources, the Secretariat aims to publish adopted texts for inclusion in The International Pharmacopoeia after each meeting of the ECSPP.
Step 15: Identify already established ICRS referred to in the monograph. Review the ICRS establishment report(s) to evaluate if the intended uses and the quantity per vial are still valid and appropriate or need to be amended or revised in view of the analytical provisions of the new standard.

Step 16: Identify newly to be established ICRS referred to in the monograph. Revert to potential donors of candidate material (Step 11) and initiate the shipment of the material to the WHO custodian organization in charge of ICRSs.

Step 17: Perform laboratory investigations to characterize the candidate material and/or to ensure the suitability of the material for its new or revised intended uses. Issue an ICRS establishment or re-establishment report. If information in the ICRS leaflet of already established ICRS has to be revised, assign a new batch number to the ICRS.

Step 18: Submit the establishment report to the ICRS Board. Start the distribution of the ICRS after the reference substance is released by the ICRS Board and the corresponding new monograph is published.

Step 19: Submit the ICRS report to the ECSPP to confirm the release of the reference standard and/or the change(s) in the leaflets.

**Omission of monographs**

Step 1: Identify monographs on medicines (or other pharmaceutical products) that are described in *The International Pharmacopoeia* but are no longer included in the WHO Model List of Essential Medicines or otherwise relevant for WHO health programmes.

Step 2: Submit the list of monographs (and other texts) proposed for omission to the ECSPP for possible approval.

Step 3: Transfer omitted texts to a publicly accessible archive section on the WHO website, together with the following note: “These monographs will neither be updated or revised, nor will the corresponding International Chemical Reference Substances be further monitored. Users will need to ensure that the product complies with current rules and regulations governing medicines and related products in their respective territories.”
Step 4: Remove the ICRS referred to in omitted monographs from the ICRS catalogue one year after the monograph has been transferred to the archive page on the WHO website.

Elaboration, revision and omission of other pharmacopoeial texts

In principle, the steps outlined above apply to all texts. Some specific texts may, however, necessitate deviations. The steps in the development of pharmacopoeial texts, however, shall always include public consultation, consideration of comments received, if appropriate, and adoption of the texts by the ECSPP.

Procedure for the development of monographs and other texts for The International Pharmacopoeia

Introduction

The process described below is designed to ensure wide consultation and transparency during monograph development and that the adopted texts are made available in a timely manner.

Subject to the availability of the necessary resources, the Secretariat aims to publish adopted monographs or general texts for inclusion in The International Pharmacopoeia after every meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations. The proposed changes to the process for the development of monographs reflect this new approach.

Monographs in The International Pharmacopoeia provide an important element of the quality dimension for the medicines (included on the basis of their efficacy and safety) in the WHO model lists of essential medicines and in WHO treatment guidelines.

Major WHO programmes such as the Prequalification Team—Medicines (funded by the Bill & Melinda Gates Foundation and UNITAID) and others funded or managed by partner organizations such as the United Nations Children’s Fund and the Global Fund to Fight AIDS, Tuberculosis and Malaria, rely heavily upon the quality specifications set out in The International Pharmacopoeia.
The procedure for the development of monographs and other texts for The International Pharmacopoeia is outlined in the Note “schedule for the adoption process” outlining the development history of a draft monograph, which is included in each working document that is circulated for comment. The phases of the development procedure are as follows.

Phase 1: Identify specific pharmaceutical products for which quality control (QC) specifications need to be developed, following confirmation by all WHO parties concerned (including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification Team – Medicines). Establish whether monographs also need to be developed for the active pharmaceutical ingredients (APIs) contained in the pharmaceutical products identified. Update the current workplan of The International Pharmacopoeia.

Phase 2: Obtain the contact details for the manufacturers of the selected APIs and pharmaceutical products, as applicable, in collaboration with all parties concerned.

Phase 3: Contact manufacturers to ask for QC specifications and samples to be provided.

Phase 4: Identify and contact QC laboratories to collaborate in the project (the number of laboratories contacted will depend on how many APIs and pharmaceutical products have been identified in Phase 1).

Phase 5: Make arrangements with the collaborating laboratories for drafting the specifications and undertaking the necessary laboratory work.

Phase 6: Search for information on QC specifications available in the public domain.

Phase 7: Perform laboratory testing, development and validation, if needed, of QC specifications.

Phase 8: Follow the WHO Expert Committee consultative process: mail draft specifications to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to specialists; provide drafts on the website.
Phase 9: Contact collaborating manufacturers to ascertain the availability of the respective substances to establish International Chemical Reference Substances (ICRS), as necessary.

Phase 10: Support the WHO host organization (European Directorate for the Quality of Medicines & HealthCare, Council of Europe) responsible for the establishment of ICRS.

Phase 11: Collect and collate the comments received during the global consultative process.

Phase 12: Discuss comments received during the consultation process with contract laboratories, WHO collaborating centres, and if relevant with the ICRS host organization; conduct additional laboratory testing to add, verify and/or validate specifications.

Phase 13: Discuss the comments received during the consultation process and test results received as feedback from the collaborating laboratories in an informal consultation with experts and specialists.

Phase 14: Recirculate draft monograph widely for comments.

Phase 15: Repeat Phases 8–15, until the agreed draft is suitable for adoption.

Phase 16: Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption. If not adopted, repeat Phases 8–14 as often as necessary. If the draft is adopted, proceed to Phase 17.

Phase 17: Incorporate all changes agreed during the discussion leading to adoption together with any editorial corrections.

Phase 18: Where necessary, also take into account any further comments that may be received after the consultation or meeting, owing to comment deadlines for recirculated texts (Phase 12 and subsequent phases) falling shortly after the relevant consultation or meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Phase 19: In all cases, confirm the amended text by correspondence with the relevant experts and/or contract laboratory before making it available on The International
Pharmacopoeia website or publishing it in a new edition or supplement of The International Pharmacopoeia.

Phase 20: Include adopted text in The International Pharmacopoeia.

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