Procedure for the elaboration, revision and omission of monographs and other texts for *The International Pharmacopoeia*

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1. Introduction

Monographs in *The International Pharmacopoeia* (1) 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) (2) 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 includes steps related to the establishment of the International Chemical Reference Substances (ICRS) referred to in analytical tests. It replaces the previous version of the document (3).

2. Elaboration of monographs

The steps of the development procedure are as follows[1],[2] :

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 (EML) (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 concerned, including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification Team – Medicines (PQT).
Step 2:	Search for relevant information on the product in the public domain, including other pharmacopoeias.
Step 3:	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 4:	Contact manufacturers of WHO prequalified medicines and/or of medicines authorized by WHO listed national regulatory systems with an appropriate maturity level [3] to request quality control (QC) specifications and samples of their products.
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 pharmacopoeias, 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.
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 for 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 9 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 organization for the establishment, storage and distribution of ICRS, the 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*. [4]
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 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.

3. 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 EML 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.

4. 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.

References

1. The International Pharmacopoeia, 9th ed. Geneva: World Health Organization; 2019.

2. Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

3. Procedure for the development of monographs and other texts for The International Pharmacopoeia. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, Forty-ninth report. Geneva: World Health Organization; 2015: Annex 1 (WHO Technical Report Series, No. 992).

[1] 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 organization for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines & HealthCare (EDQM). The steps are therefore described from the perspective of all partners involved.

[2] The steps are listed in their chronological order. However, certain steps may overlap during the development of monographs and other compendial texts.

[3] It is intended to refer in a future version of the document to the WHO Global Benchmarking Tool (GBT), which is currently under discussion.

[4] 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.