EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES (EDQM)

BIOLOGICAL STANDARDISATION

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

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INTERNATIONAL STANDARDS FOR ANTIBIOTICS

International Standards for Antibiotics General Procedure

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Distribution

For action:

For information :

ECBS-WHO Expert Committee on Biological Standardisation - WHO
ISA001 Vancomycin Hydrochloride Study
ISA002 Nystatin Study
ISA003 Amphotericin B Study
ISA004 Gramicidin Study

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Summary

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1. AIM

The aim of the ISA programme is the establishment of International Standards for Antibiotics used in human and veterinary medicine by the EDQM on behalf of the WHO.

2. SCOPE

This procedure describes how the WHO International Standards for Antibiotics (ISA) programme is developed.

This procedure is addressed to persons involved in ISA establishment.

3. STAKEHOLDERS AND PARTNERS IN THE PROGRAMME

3.1 THE STAKEHOLDERS

- The national competent authority or agency supporting the ISA programme

- WHO Headquarters, Geneva (QSB/ECBS)

- EDQM, Council of Europe, Strasbourg

3.2 THE PARTNERS IN THE PROGRAMME

3.2.1 THE APPROVAL COMMITTEE: THE EXPERTS COMMITTEE ON BIOLOGICAL STANDARDIZATION (ECBS) / WHO

The ECBS is composed of scientists from national control agencies, academia, research institutes, public health bodies and the pharmaceutical industry acting as individual experts and not as representatives of their respective organizations or employers.

The role of the approval committee is:

- to decide the start of new ISA establishment studies

- to approve the final project report thus establishing and adopting the standard.

The ECBS meets on an annual basis and directly reports to the Executive Board (WHO) between annual meetings, the activities may be done by correspondence.

3.2.2 THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES (EDQM)

EDQM provides the secretarial support and is charged with the administration and coordination of the programme including scientific studies, procurement, material handling, production, storage and distribution of ISA.

3.2.3 THE PARTICIPANTS IN THE ISA ESTABLISHMENT STUDY

EDQM invites national control laboratories, academic research laboratories, organizations or agencies having expertise in this field of interest to participate in ISA establishment studies on a voluntary basis.

Participants will be required to agree not to publish information on a proposed ISA without the prior agreement of the WHO and certainly not until it has been adopted and officialised in the list of WHO ISA.

3.2.4 THE MATERIAL PROVIDERS

EDQM approaches manufacturers of suitable products for donation of materials along with relevant information on quality and safety.

4. THE STEPS INVOLVED IN AN ISA ESTABLISHMENT STUDY

4.1 GENERAL RULES

- All studies/experiments are carried out taking into account:
  - the WHO guideline for the preparation and establishment of reference material and reference reagents for biological substances (WHO,TRS 626,1978, Annex 4, 101-140)
  - the WHO guidelines for the preparation and establishment of international and other standards and reference reagents for biological substances (WHO, TRS 760, Annex 3, 39-81)
  - the WHO recommendation for the preparation, characterization and establishment of international and other biological reference standards (WHO, TRS 800,1990, 181-213, revised 2004)
  - relevant international guidelines such as ISO Guidelines and State-of-the-art relevant procedures
- ISA are established as primary reference standards, which are subsequently used to establish national or regional secondary standard to be used for routine tests and assays.
- Replacement batches of ISA are established with reference to the current international standard to ensure continuity of the International Unit (IU).

4.2 STEP 1: INITIATION AND APPROVAL OF ISA ESTABLISHMENT PROJECT

- The decision to prepare a new ISA is taken by WHO/ECBS at the request of EDQM or any other relevant stakeholder.
- Replacement of an ISA batch is undertaken following a request from EDQM.

A working programme is prepared by EDQM. The working programme for the forthcoming year is submitted to ECBS/WHO by 1 September of the current year.

As soon as approved by ECBS (see 3.2.1), EDQM initiates the procedure.

4.3 STEP 2: PROCUREMENT OF MATERIALS AND INFORMATION, INVITATION OF STUDY PARTICIPANTS AND PROTOCOL ESTABLISHEMENT

EDQM contacts possible suppliers and participants, including all members and observers at ECBS, who have an expertise in the field of microbiological assay of antibiotics.

A protocol is then prepared by a "study director" from EDQM according to data and comments received from participants, if any.

4.4 STEP 3: LABELLING OF SAMPLES AND DISPATCH OF SAMPLES AND PROTOCOL TO THE PARTICIPANTS

EDQM:

- labels the samples (without mentioning the nature and origin of candidate(s) ISA)
- manages the administrative documents necessary for sending the protocol and samples under relevant shipping conditions according to the transport and/or drug control regulations
- ships them together with the protocol and reporting sheets. The protocol is also sent to the participants by e-mail
- informs the recipient of the sample of the shipment date to ensure smooth reception.

An Acknowledgment of Receipt is sent together with the samples and must be returned by the recipient to EDQM.

As often as possible, packages are delivered according to the door-to-door principle.

4.5 STEP 4: EXPERIMENTAL PHASE

Participants carry out the experiments and send the required data to EDQM according to the protocol within the timeframe. Results are returned both in electronic format and as a signed paper copy. Each participant is asked to report details of the assay method used (e.g. details of test organisms).

4.6 STEP 5: RAW DATA COLLECTION AND CODING

EDQM collects the results and codes the laboratories for anonymity.

4.7 STEP 6: SCIENTIFIC AND STATISTICAL EVALUATION

Before including data in the statistical evaluation, the study director verifies protocol compliance and validity of the reported data. If results have to be excluded, a justification is given in the report.

In general, the EDQM statistician performs the statistical evaluation of the data from the ISA establishment study. If she/he is not available, EDQM can charge an external statistician with this task.

The statistician writes a report on his/her evaluation, which becomes part of the study report. If data have to be excluded, a justification is given in the report. Identification of participants is coded.

4.8 STEP 7: PRELIMINARY REPORT

The study director compiles a preliminary report.

If necessary, deviations from the protocol as well as details concerning the methods used are included.

4.9 STEP 8: COMMENTING THE PRELIMINARY REPORT

The preliminary report is sent to the participants. Each participating laboratory is informed individually of its identification code as used in the report. The participants check the completeness and the accuracy of the reported data and whether they agree with the study conclusion. Any comments must be received within the given timeframe (2 weeks).

4.10 STEP 9: FINAL REPORT

The study director finalises the report. The comments of the participants are discussed and might be incorporated into the final report where appropriate. Any reasons for not integrating comments are communicated to the participant who made the comments.

If necessary, EDQM organises a teleconference with participants to settle unresolved issues in the final report.

EDQM sends the final report to the participants for information and if major changes (modification of the assigned value, exclusion of data) are included, asks them to approve it by correspondence. The response is requested in a given timeframe otherwise approval is assumed.

4.11 STEP 10: APPROVAL COMMITTEE

EDQM submits the final reports to the ECBS for adoption.

4.12 STEP 11: RELEASE OF ISA

When a substance has been adopted as an ISA, EDQM prepares a leaflet for distribution and related MSDS and the ISA is released.

4.13 STEP 12: ANNOUNCEMENT OF ISA

EDQM makes the public aware of the release of the ISA through suitable means.

4.14 STEP 13: PUBLICATION OF RESULTS

The establishment report is published in *Microbiologicals** or any other relevant publications.

5. ACTIVITIES FOLLOWING THE CONCLUSION OF AN ISA ESTABLISHMENT STUDY

The monitoring of the quality of an established ISA is undertaken.

6. ABBREVIATIONS

ECBS:	Expert Committee on Biological Standardization
EDQM:	European Directorate for the Quality of Medicines
ISA:	International Standards for Antibiotics
MSDS:	Material Safety Data Sheets
QSB:	Quality assurance and Safety of Biologicals
TRS:	Technical Report Study
WHO:	World Health Organization

* *to be confirmed*