

## Frequently Asked Questions about collaborative trials to establish International Standards for Antibiotics (ISAs)

### 1. What is the aim of the EDQM ISA Programme?

The aim of the ISA programme is the production of International Standards for Antibiotics which are used in the quality control of antibiotics for human and veterinary use. The ISA programme is co-ordinated by the EDQM on behalf of the WHO.

The term “production” of reference standards is used according to the definition given in the ISO Guide 34 for “production of a reference material”: *all necessary activities and tasks leading to a reference material (certified or non-certified) supplied to customers*  
*NOTE: production of a reference material includes production planning, production control, material handling and storage, material processing (also referred to as “manufacturing” or “preparation”), assessment of homogeneity and stability, issue of statements and post-distribution service of the reference materials. It can include characterization, assignment of property values and their uncertainties, authorization and issue of certificates for certified reference materials.”*

### 2. What are ISAs?

*The International Pharmacopoeia* provides specifications and analytical methods to evaluate the quality of essential medicines, notably antibiotics.

ISAs are reference substances for use as primary standards in microbiological testing of antibiotics (usually described in *The International Pharmacopoeia*). The standards are certified as suitable for their intended use by the WHO Expert Committee on Biological Standardization.

ISAs can also be used by regional or national pharmacopoeias to establish secondary standards.

ISAs should not be used as working standards in routine assays as they are produced in limited quantity.

Note: the EDQM has established secondary standards for some antibiotics (e.g. colistin sulfate, erythromycin etc). Please refer to the EDQM catalogue (<http://crs.edqm.eu/>) for further information.

### 3. Why are collaborative trials needed to establish ISAs?

When a reference standard is to be used in an assay determination it may become necessary for several collaborating laboratories to examine the proposed candidate material, following a detailed protocol. The results obtained are used to assign a content value to the standards.

### 4. Who can participate in collaborative trials and how?

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

Laboratories involved should have a recognised Quality Management System and be proficient in the technique to be used during the establishment, eg they should be ISO 17025 accredited, be a WHO pre-qualified laboratory, have a GMP certificate etc.

Laboratories wishing to contribute or ask questions can send an e-mail to the following address: [ISA\\_studies@edqm.eu](mailto:ISA_studies@edqm.eu) for further guidance.

### **5. Who will organise the collaborative trials to characterise ISAs?**

At the 56<sup>th</sup> meeting of the WHO Expert Committee on Biological Standardization (Geneva, October 2005), the European Directory for Quality of Medicines & HealthCare (EDQM) of the Council of Europe was given a mandate for the establishment, storage and distribution of the WHO's ISAs, which includes the organisation of collaborative trials and the evaluation of their results. This partnership allows the WHO to be supported by the EDQM's technical expertise and experience of in establishing primary reference standards.

### **6. Which analytical tests have to be performed in a collaborative trial?**

For each collaborative trial, a protocol is prepared by the EDQM. Participants are obliged to follow the protocol instructions strictly. The analytical method is the microbiological assay of antibiotics.

All studies/experiments are carried out taking into account:

- ✓ The WHO "Recommendations for the preparation, characterization and establishment of international and other biological reference standards" (revised 2004; WHO, TRS 932, 2006, 73-131),
- ✓ The ISO Guide 34 "General requirements for the competence of reference material producers".

### **7. What are the main steps in the establishment of ISAs?**

Once the working programme has been approved by the WHO Expert Committee on Biological Standardization, the EDQM will invite potential participants.

Before the analytical work, the EDQM will distribute the draft protocol to collect their comments, if any.

Samples will be dispatched together with a protocol giving details about the analytical tests. The protocol will contain an EDQM contact person to be consulted in case of further questions.

EDQM will evaluate the results of the study and issue a preliminary report. This report is sent to the participants for comments. After this, the final report is issued.

The report will make a recommendation on the suitability of the candidate material and a proposed assigned value. Based on this report, the WHO Expert Committee on Biological Standardization will finally adopt the reference standard.

### **8. Would the name of my laboratory be known if I obtain invalid results?**

All participating laboratories are listed in alphabetical order in the establishment report. Laboratories are referred to by their randomly assigned code-numbers, not necessarily corresponding with the order in which the participants are listed so that individual results cannot be identified from the report. No other action is taken and no one is alerted regarding results. Moreover all results/data from individual laboratories are kept confidential by the EDQM.

### **9. Which collaborative trials have already been scheduled?**

The EDQM and the WHO have identified priorities for the establishment of ISAs. However, as our programme relies substantially on donations of candidate material, we are not able to set up a long-term work plan.

**10. Do the analytical methods of the protocol have to be validated by the participants?**

The test methods given in the protocol are pharmacopoeial methods, which are considered to be validated. A validation of the test methods by the analyst is not required. However, each participant should make sure that the analytical method fulfils the validity criteria as prescribed in the relevant compendia.

**11. What is the timeline for delivery of results?**

The participating laboratory should aim to report the results to the EDQM within six weeks after receiving the samples.

**12. Do participating laboratories benefit from their involvement?**

Within six months of its approval by the WHO Expert Committee on Biological Standardization, the establishment report is published in *Pharmeuropa Bio & Scientific Notes*. The publication contains the names of all participating laboratories.

Participating laboratories can request an official attestation demonstrating their proficiency in the technique used for the establishment study. This attestation can be used to support demonstration of competence in the framework of the Quality Management System (e.g. ISO 17025:2005 - §5.9.1). Should you need this attestation, please send an e-mail to the following address: [ISA\\_studies@edqm.eu](mailto:ISA_studies@edqm.eu).

There is no provision for any financial compensation in the programme.

**13. I would be interested in participating but my laboratory has not been invited to participate as mentioned in §4.**

The EDQM welcomes any participants wishing to join the programme. If you are interested in participating in the ISA collaborative studies, please send an e-mail to the following address: [ISA\\_studies@edqm.eu](mailto:ISA_studies@edqm.eu).

**14. Can a laboratory withdraw its contribution?**

Laboratories may withdraw their participation whenever they wish.

In such a case, please send an e-mail to the following address: [ISA\\_studies@edqm.eu](mailto:ISA_studies@edqm.eu) to notify us of your decision.