

Annex 2

Guidelines for national authorities on quality assurance for biological products

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1. Scope

This document describes measures for assuring the safety and efficacy of biological products intended for use in humans. Its aim is to provide general guidelines for national health authorities on quality assurance for biological products, except those used solely as *in vitro* diagnostic agents. The concepts and principles have been harmonized with those of the Requirements for Biological Substances and other related sets of recommendations published by WHO (1). Though it is difficult to provide a set of guidelines applicable to all national situations, an attempt has been made to cover a range of possibilities; the principles on which this document is based may assist in the development of national guidelines.

2. Introduction

Since the publication by WHO in 1981 of a document entitled “The national control of vaccines and sera” (2), it has become apparent that it would be helpful to provide updated guidance for countries wishing to develop or improve quality-assurance procedures for biological products. In addition, technological developments in the production of biologicals and the availability of new analytical methods for determining their quality

have made evident the need for a further revision of the Requirements for Biological Substances No.1 (General Requirements for Manufacturing Establishments and Control Laboratories), published in 1966 (3). The present guidelines reflect the decision to combine parts of these two documents into a single text.

National regulatory authorities have the duty to ensure that available pharmaceutical products, whether imported or manufactured locally, are of the required quality. This is particularly difficult for biological products, the quality of which cannot be established entirely by tests on the material in the final container. The national authority has the responsibility to confirm that the manufacturer is adhering to the approved standards of good manufacturing practice and to national and other requirements for manufacture and quality control specific to the product. The mechanism by which national authorities confirm the assurance of quality provided by the manufacturer may depend on the resources available and whether the product is manufactured locally or imported.

In general biological products are distinguished from other drugs by being derived from living organisms (ranging from normal or genetically modified microorganisms to humans), and frequently have a complex molecular structure. They require special quality considerations because of the biological nature of: (a) the starting materials, and/or (b) the manufacturing process, and/or (c) the test methods needed to characterize batches of the product.

Recognizing these difficulties and the need for international harmonization of quality standards, WHO, largely through its Biologicals unit, has a number of activities related to the quality assurance of biological products used for the diagnosis, prevention and treatment of diseases. These include: (a) publishing in the WHO Technical Report Series the reports of expert groups, which may include documents such as this one that constitute requirements or guidelines for use by national authorities; (b) organizing the distribution of International Standards and other reference materials for biological substances, which allow the characterization and assay of products in terms of internationally accepted units; (c) providing advice on the preparation of national reference materials; (d) advising and assisting Member States in the establishment and functioning of structures for national control purposes, e.g. by organizing visits by experts and assisting with programmes of training and research in relation to these activities; and (e) arranging scientific meetings to provide an up-to-date and scientifically valid consensus on topics relating to quality assurance that are generally applicable to Member States throughout the world.

Developments in biological products have been extremely rapid in recent years, and the potential of such products for improving health care on a global scale is immense. There is an urgent need to match technological advances with appropriate mechanisms for assuring the quality of the products.

3. General considerations

The quality, safety and efficacy of a biological product are the prime responsibility of the manufacturer; however, the national health authority of each Member State is responsible for establishing procedures for assuring that biological products intended for use in the country are of adequate quality, safety and efficacy. This responsibility should have a firm statutory basis backed by legislation. Marketing approval for a biological product should be granted by a national control authority (NCA), which should also be responsible for continued post-marketing monitoring. In carrying out these activities, the NCA should make use of expert committees and technical advisers, and have access to laboratory facilities.¹

Individual Member States should have written standards, both general and product-specific, for biological products available for use in their countries. These should be based on contemporary standards, such as those available from WHO, and harmonized as far as possible with those of other Member States. For newly developed products, WHO, national and pharmacopoeial requirements may not have been developed and the NCA will need to agree on specifications with the manufacturer on a case-by-case basis.

In countries where biological products are manufactured, the NCA should have appropriate expertise to evaluate the adequacy of the manufacturer's establishment and facilities, starting materials, production processes, control-test procedures and product specifications, to determine whether they meet international and/or national requirements. These control activities should be fully independent of those of the manufacturer; ideally the national laboratory facilities should form a single administrative unit designated as the national control laboratory (NCL). The NCL may be administered directly by, or on behalf of, the NCA.

In countries where biological products are not manufactured, alternative approaches may be acceptable for assuring the safety and efficacy of these products (see section 8). However, an approval process limited to a mere listing of facilities and products would not be considered adequate.

In view of the complexity and cost of certain resources needed for control testing, it may be unavoidable in certain cases to share such resources with the manufacturer or an academic institution, or to rely on the resources of an NCL in another Member State.

National control authorities should, whenever appropriate, exchange information on safety issues, within the constraints of confidentiality, in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4).

¹ In this document reference is made only to the role of the NCA with respect to biologicals; in practice it is to be expected that the NCA will have responsibility for all pharmaceutical products.

4. **Structure of a national control authority for biological products**

In countries where biological products are manufactured, the health authorities should establish and maintain a competent NCA and NCL. It is recommended that the NCA should make use of independent expert advisers and advisory committees with appropriate expertise and have access to testing facilities, such as those of the NCL, to support decision-making. In some instances a multinational or regional structure may be more efficient.

4.1 ***Personnel***

The personnel of the NCA and the NCL should include person(s) qualified and experienced in the control of biological products and experts in all appropriate disciplines. The qualifications and experience of the staff at all levels should be appropriate to the review and control activities required for the range of biological products to be controlled. It is advantageous for the director of the NCL to report directly to the director of the NCA.

Contact between NCA and NCL personnel and scientists working in related fields will be beneficial for exchanging ideas and discussing techniques, problems and analytical results.

All staff of the NCA and NCL should receive suitable training through active training programmes, covering both the technical and the administrative aspects of control procedures.

Encouragement of research activities within the NCL will both lead to the development of better control methods and help the laboratory to retain an interested, efficient and highly qualified staff.

4.2 ***Administration***

The NCA should have established procedures for the receipt and review of manufacturers' submissions and for testing samples provided in support of applications. On completion of the review procedures, which include the evaluation of detailed reports (see sections 5 and 6), the NCA issues a notice of approval or disapproval to the manufacturer. It may also issue notices of suspension or revocation of approval. Consideration should be given to making available appropriate legal expertise in support of this activity.

The NCA should maintain adequate filing and archiving facilities, such that all submissions, evaluations, records and correspondence are available and kept up to date. Attention should be given to the need to maintain commercial confidentiality.

The NCA and NCL should possess, or have access to, library facilities appropriate to their fields of activity. The documents available should include: current national and international requirements for products that

are manufactured locally, relevant international requirements for biological substances, and other relevant specifications and recommendations published by WHO or other bodies.

4.3 ***Good manufacturing practices (GMP) inspectorate***

The NCA should have access to suitably qualified inspectors who are independent of manufacturers. The purpose of inspections will be to ensure compliance of each manufacturer's facilities and procedures with the principles of GMP as described in WHO publications (5, 6) and with the requirements and/or conditions for the approval for the product concerned. Guidelines are available for conducting inspections of manufacturers of both drugs and biologicals (7). Reciprocal arrangements for international inspection such as those of the Pharmaceutical Inspection Convention of the European Free Trade Association (8) may be used, as may the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4).

5. **Procedures for approval of manufacturers and products**

Approval or licensing of a manufacturing establishment for production of biological products should be granted only if the manufacturer complies with the principles of GMP (5, 6), as confirmed by inspection.

Approval or licensure of a given biological product will be given by the NCA when it is satisfied that the product conforms to the relevant national and/or international requirements, including the manufacturer's specifications applicable to the product. In order to evaluate the safety and efficacy of a biological product, the NCA should review the following detailed information before granting an approval.

5.1 ***Information on the manufacturing establishment***

The manufacturer should provide sufficient information to demonstrate compliance with the principles of GMP (5, 6), including the existence of adequate quality-assurance systems. Plans, diagrams, flow charts and texts may be used to convey the necessary information in relation to (but not limited to):

- personnel:
 - qualifications and experience,
 - organization and reporting relationships,
 - training schedules and recording systems;
- location and construction of the buildings used for manufacture and control;
- flow of raw materials, personnel and manufactured product through the facility;
- animal facilities;
- air, water and steam systems and power supply;
- drainage and effluent systems;

- segregation of operations;
- lists of major equipment;
- maintenance schedules for equipment and building services;
- cleaning schedules;
- quality-assurance and quality-control procedures;
- storage and quarantine facilities and procedures for:
 - raw materials,
 - packaging materials,
 - in-process and bulk materials,
 - final product;
- validation procedures;
- documentation and record-keeping systems;
- labelling and packaging facilities and procedures;
- recall and retrieval procedures.

To be certain that the buildings, facilities, personnel, procedures and practices comply with the description in the licence application, the NCA should arrange for the inspection of the manufacturer before granting the licence. The inspector(s) selected should be independent of the manufacturer and have sufficient expertise to conduct a meaningful review, in accordance with section 4.3, of the GMP system in use (including buildings, facilities, procedures, personnel and quality assurance).

5.2 ***Information on the product***

The manufacturer should provide sufficient information to demonstrate the safety and efficacy of the product as manufactured and controlled in the establishment described above. The NCA should request from the manufacturer a critical evaluation of the procedures adopted for manufacture and control of the product and of preclinical and clinical studies relevant to its proposed use. The submission should include the following details, if appropriate:

- source materials (e.g. microorganisms, blood/plasma donations, cells/cell substrates, pollen), including their specifications and the tests used to demonstrate compliance with the specifications;
- raw materials and packaging materials, including their specifications and the tests used to demonstrate compliance;
- methods of manufacture, including a description of seed-lot and cell-substrate systems used, together with in-process, bulk and final product specifications and the tests employed to demonstrate compliance;
- demonstration of consistency of manufacture, which normally comprises the results of tests on a minimum of three satisfactory and consecutive production batches of a size corresponding to that contemplated for routine production;
- any proposal for reprocessing of the product;
- stability studies undertaken to justify the proposed validity period for the product under the indicated storage conditions;

- labels and package inserts;
- documentation used in the manufacturing and control procedures, including standard operating procedures and protocols containing details of production and quality-control testing;
- reports of preclinical studies;
- clinical trial data;
- a list of countries in which the product is approved for use.

The nature and extent of pre-licensing testing undertaken by the NCA should reflect any particular quality-assurance considerations relevant to the product; as a minimum, the NCA should undertake tests to evaluate its safety and efficacy. It may also perform chemical, physical and biological tests additional to those specified in national or international requirements.

6. The national control laboratory

The size of facilities and number of staff of the NCL will depend on the nature and extent of the quality control required. Some guidance is available in the *Manual for the design, equipping and staffing of facilities for production and quality control of bacterial vaccines* (9).

6.1 Laboratory testing and evaluation

The NCL (or equivalent) should be able to perform all necessary tests on samples of source materials and of intermediate, bulk and finished products. This will require specialized facilities and equipment. If the NCL is on a site where biological products are manufactured, national control activities should be independent of control activities associated with manufacture or production.

The NCL's responsibilities should include some or all of the following activities:

- provision of advice to the NCA on technical matters relevant to the approval of products and manufacturing establishments;
- evaluation of manufacturers' preparative and analytical procedures, standard operating procedures, validation experiments and batch protocols;
- pre-licensing control testing of samples of batches, in particular for ascertaining consistency of production, as well as testing for batch release;
- evaluation of shelf-life specifications and expiry dates of final lots on the basis of the manufacturer's thermal stability tests and stated conditions of storage, and experimental verification of stability;
- development, evaluation, establishment and implementation of testing procedures and release criteria;
- review of reports of quality defects in distributed material, retesting if appropriate, and provision of advice on whether the preparations should remain on the market or be withdrawn;

- undertaking of research in relation to the above activities (which may involve collaboration with manufacturers).

In order to fulfil its responsibilities, the NCL should have the authority to demand appropriate samples (e.g. of starting materials, intermediate products and finished biologicals) from manufacturers. The samples should be properly labelled and portions should be kept for future reference.

The control laboratory should maintain adequate analytical records of all samples examined, including:

- the results of tests performed, including original observations and calculations, relating to compliance with the established specifications;
- the date and signature(s) of the person(s) who performed the quality-control tests; and
- a final review, with a dated endorsement of the final decision by a responsible person.

6.2 ***Establishment of national reference materials for biological substances***

WHO has published guidelines on the preparation, characterization and establishment of international and other reference materials (*10*), and a list of International Standards, International Reference Reagents and International Reference Preparations is available (*11*).

It may be desirable for appropriate national (secondary) reference materials, calibrated against international reference materials, to be established by the NCL and made available to manufacturers. However, a multinational or regional approach to the establishment and supply of secondary reference materials may be more efficient. The secondary reference materials should be used in the routine laboratory testing of biological products. Their use permits the expression of *potency* in International Units, and in some cases they may be useful in confirming the *identity* of biological products.

6.3 ***Other activities of the national control laboratory***

The NCL, or the laboratories providing the services of an NCL, should devise effective internal control measures to permit the evaluation of their reliability in performing all tests. The inclusion of reference preparations and coded replicate samples in test procedures, simultaneous independent testing, and routine checks on the sensitivity and calibration of instruments are necessary as part of good laboratory practice for the NCL. The NCL should, if possible, participate in collaborative studies with other NCLs and other relevant laboratories to enhance its expertise.

7. **Post-licensing monitoring of products**

7.1 ***Product release***

At the time a product is approved, the NCA should decide whether controls involving the NCA are to be applied to release of batches of the product. This decision will be influenced by the nature of the product. Controls will usually be imposed on complex products and on those obtained by complex manufacturing procedures. The control system may involve the following activities and may be reviewed and revised once satisfactory and consistent production has been demonstrated:

7.1.1 Testing of samples of intermediate, bulk or final product, to confirm compliance with the requirements and agreed specifications. The nature and frequency of the tests to be carried out are decided by the NCA.

7.1.2 Evaluation of the manufacturer's protocols for manufacture and control of each batch. Examples of model summary protocols are annexed to the individual Requirements for Biological Substances published by WHO. The critical review of batch protocols by the NCA is a most important part of the control of biological products. The information provided should make it possible to review the manufacture and testing of each batch of a particular product, including all required in-process controls and control tests on final products, to confirm compliance with the approved specifications.

7.2 ***Inspections***

Periodic inspections of the manufacturing facility should be carried out on behalf of the NCA to assure continued compliance with GMP and with the specifications established for the product at the time of approval. Records of complaints and reports of adverse reactions should be examined.

7.3 ***Post-marketing surveillance***

The procedures described in sections 7.1 and 7.2 above do not preclude the need for a post-marketing sampling and surveillance system. Countries should establish a national system for the post-marketing surveillance of biological products. Clinicians and other health workers should be encouraged to report to manufacturers and NCAs unexpected adverse events occurring after administration of biological products. The manufacturers and the NCAs should assess these reports and, in consultation with each other, attempt to evaluate their significance. This assessment may require the testing of products already released and inspection of production and control facilities. If an imported product is associated with adverse reactions, the manufacturer and, where appropriate, other NCAs and WHO should be notified.

Guidance for operating a monitoring system for adverse reactions is provided in a report published by the Council for International Organizations of Medical Sciences (12).

7.4 ***Recall and revocation***

NCA should have a system for enforcing the recall of batches, revoking approvals, and communicating such decisions to users and to the NCAs of any countries importing the product.

7.5 ***Approval of manufacturing changes***

Any significant change to the manufacturing establishment, source materials, production process, quality-assurance procedures, product specifications or labelling should have the prior approval of the NCA.

7.6 ***Approval of new indications***

NCA should require that significant proposed changes in product indications or use be submitted by manufacturers for evaluation and approval.

8. **Procedures for approval of imported products**

The national authorities of countries wishing to import biological products could simplify the licensing formalities, and reduce the need for testing, by accepting certificates, issued by the responsible authorities in the country of manufacture, stating that the quality of the product meets a certain standard. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (4) and GMP texts (5, 6), with the inclusion of the procedures described in this section, provide a suitable basis for such a mechanism. For the purpose of this Certification Scheme, "biological product" refers to a product presented in its finished dosage form and to the bulk material that is processed to produce this dosage form.

8.1 ***Participating Member States***

Each Member State participating in the Certification Scheme should communicate to WHO the name and address of the department of its NCA dealing with biological products and, if appropriate, any significant reservations relating to its participation. WHO would then notify all other Member States.

Exporting Member States participating in the Certification Scheme should ensure that:

- approval of biological products is subject to appropriate control testing by the NCA to assure safety and efficacy, and adequate facilities are available for such testing;
- the manufacturer conforms to requirements for GMP and quality assurance of biological products as recommended by WHO, or to equivalent national standards;
- the NCA conducts appropriate inspections, including, for example, examination of records and samples, to ensure that manufacturers conform to these requirements;
- the inspectors in the service of the NCA have appropriate expertise.

Exporting Member States participating in the Certification Scheme should, whenever possible, ensure that International Nonproprietary Names (INN) are used on certificates and for labelling the biological product.

8.2 ***Certification of products***

Biological products exported under the Certification Scheme should be certified by the NCA of the exporting Member State by means of certificates to be sent to the NCA of the importing Member State. The importing Member State would then either license the product or make licensing conditional on the submission, and approval, of supplementary data.

The issue of certificates for a biological product would be subject to the conditions set by the NCA of the exporting Member State. Certificates would, however, be expected to state that:

- the product is approved for use within the exporting Member State (if not, the reason should be given); and
- the manufacturing establishment in which the product is produced is inspected at suitable intervals to check that the manufacturer conforms to the principles of GMP (5, 6) and quality assurance (as defined in the present guidelines).

For many biological products, certification on an individual lot basis is necessary because of the difficulty of controlling starting materials and ensuring that batch-to-batch variation is within acceptable limits.

Suggested model certificates for biological products are given in Appendices 1 and 2.

8.3 ***Requests for additional information***

Additional information may be requested by the NCA of the importing Member State from the NCA of the exporting Member State. This information may be provided directly by the NCA, or through the manufacturer, and may include:

- details of the implementation of requirements for GMP and quality assurance of biological products;
- information on control tests performed on the product by the NCA of the exporting Member State;
- the names and functions of the persons officially designated to sign release certificates for individual batches of the product;
- copies of all documentation and labels that are supplied with the product on packaging materials and package inserts and that have been approved by the NCA in the exporting Member State, together with the date(s) on which such approval was accorded.

Information on general and specific standards for quality assurance of the biological product to be exported may also be requested if so required by

the legislative provisions of the importing Member State. The consent of the manufacturer to the provision of such information should be obtained by the NCA of the exporting Member State.

8.4 *Reporting of defects and adverse reactions*

Defects may occur in the quality of biological products imported under the Certification Scheme. If they are considered to be of a serious nature by the importing country, and are not attributable to local conditions of storage and transport, the NCA of the importing country should notify the NCA of the exporting Member State and provide the relevant data. Adverse reactions of unexpected severity or frequency should also be notified to the NCA of the exporting country. Similarly, if the NCA of the exporting Member State discovers quality defects or receives reports of unexpected adverse reactions, it should inform the NCA of the importing Member State of any action taken.

8.5 *Procedure for testing imported biological products*

Countries wishing not to rely solely on the certification scheme described in sections 8.1-8.4 may consider implementing an abridged version of the system of control applicable to the NCA of the country of manufacture, as described in sections 4-7. The system may include a review of information on the manufacturing establishment (as described in section 5.1) and on the biological product to be imported (as outlined in section 5.2), in order to assess its safety and efficacy. If adequate facilities and personnel of appropriate expertise are available, pre-licensing testing may be performed as described in section 7.1.1, although intermediate samples may not be available. Additionally, the NCA of the importing country may, if necessary, perform control tests on the biological product on a batch-to-batch basis, to obtain assurance regarding safety and efficacy, including the possibility of defects occurring during shipment.

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Appendix 1
Model certificate of approval of a biological product¹

Name and dosage form of product: _____

Manufacturer and/or, when applicable, person responsible for placing the product on the market: _____

Address(es): _____

It is certified that:

- This product has been authorized to be placed on the market for use in this country.²

Number of licence and date of issue (if applicable):²

The enclosed documents constitute the complete text of all labelling and prescribing information authorized for use in this country.²

or

- This product has not been authorized to be placed on the market for use in this country for the following reasons:

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good manufacturing practices³ and other relevant requirements published by WHO, in respect of products to be sold or distributed within the country of origin or to be exported.

Name of designated authorized person (typed) _____

(Signature of designated authorized person) (Place and date)

¹ This certificate is intended to define the status of the biological product and its manufacturer in the exporting and manufacturing country. It is issued by the competent national authority in the exporting country in response to a request by the competent national authority in the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required. The certificate is intended to be product-specific, since confusion will inevitably arise if information relating to different products, or even different dosage forms of the same product, is attached to the same certificate; whenever possible, International Nonproprietary Names (INN) or national nonproprietary names should be used.

² Delete as appropriate.

³ Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No.823), Annex 1; Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No.822), Annex 1.

Appendix 2
**Model certificate for the release of a lot or lots of
a biological product**

The following biological product _____, produced by _____¹
in _____,² whose lot numbers appear on the labels of the final
containers, meets all national requirements (_____³)
and is manufactured in accordance with the requirements for good
manufacturing practices⁴ and (if applicable) the product-specific
requirements published by WHO.

Lot number

Expiry date

_____	_____
_____	_____
_____	_____
_____	_____

As a minimum this certificate is based on examination of the
manufacturing protocol.

Address of the National Control Authority or Laboratory _____

Name of the Director of the National Control Authority or Laboratory
(or representative)

Signature _____

Date _____

¹ Name of manufacturer.

² Country.

³ Reference to appropriate document.

⁴ Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1; Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 1.