

Annex 1

Regulation and licensing of biological products in countries with newly developing regulatory authorities

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1. **Introduction**

National health authorities have the duty to ensure that available pharmaceutical products, whether imported or manufactured locally, are of good quality, safe and efficacious. This is particularly difficult for vaccines and other biological products, the quality of which cannot be established entirely by tests on the material in the final container. A national control authority should therefore be established that is responsible for ensuring that the manufacturer is adhering to approved standards of good manufacturing practice and quality assurance specific to the product. The procedures through which the national control authority confirms the assurance of quality provided by the manufacturer will 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 fluids and tissues derived from various animal and human sources) 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.

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

2. **Scope**

The aim of this Annex is to provide guidance for newly developing national control authorities that may have limited resources to license and regulate biological products, including vaccines. It describes the responsibilities of such authorities and manufacturers and provides references to relevant WHO publications relating to their structure and activities. References to more detailed technical requirements published by WHO, specific for various products including vaccines, are also provided (*1*, Annex 7).

Much of the material included in this Annex is drawn from guidelines previously published by WHO in the reports of the WHO Expert Committee on Biological Standardization and the WHO Expert Committee on Specifications for Pharmaceutical Preparations (see, in particular, *1*, Annex 2; *2*, Annex 3; *3*, Annexes 5 and 6).

3. **General considerations**

The safety, quality and efficacy of a biological product are primarily the responsibility of the manufacturer; however, the national control authority of each country 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 (licensing) for a biological product should be granted by a national control authority, which should also be responsible for continued monitoring after licensing. In carrying out these activities, the authority should make use of expert committees and technical advisers and have access to laboratory facilities for the testing of in-process and final product samples.

Countries should have written standards, both general and product-specific, for biological products available for use in them. These should be based on up-to-date standards, such as those available from WHO, and harmonized as far as possible with those of other countries. For new products, WHO, national and pharmacopoeial requirements may not have been established, and the national control authority will need to agree on specifications with the manufacturer on a case-by-case basis. In such cases, WHO or the authority in the country of origin could be consulted and their advice requested.

In general terms, the national control authority should be vested with legal powers to:

- (a) issue, vary and revoke licences for biological products on grounds of quality, safety and efficacy;
- (b) secure the subsequent safe and effective use of each product by controlling, under the terms of the product licence, the content of all labelling (including package inserts, associated prescribing information and advertising) and the channels through which the product may legitimately be supplied; and
- (c) inspect and license all manufacturing premises and importing agents and, where applicable, wholesalers and distributors, hospital dispensaries, independent pharmacies and other retail outlets to ensure that they comply with the relevant regulations and guidelines.

In countries where biological products are manufactured, the national control authority should have the 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. Guidelines for national control authorities on quality assurance for biological products have been published by WHO (*1*, Annex 2).

Control (laboratory) activities should be fully independent of those of the manufacturer so as to ensure that the national control authority

undertakes its tasks in an independent, authoritative and impartial manner. In some countries, the national laboratory facilities may constitute a separate entity called the national control laboratory. In this case, the laboratory should be administered directly by, or on behalf of, the national control authority.

In countries where biological products are not manufactured, alternative approaches can be defined, e.g. the WHO Certification Scheme (2, Annex 3) for assuring the safety, quality and efficacy of such products (see section 6). 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 facilities needed for control testing, it may be unavoidable in certain cases that the authority will have to share such facilities with the manufacturer or an academic institution, or to rely on those of an authority or laboratory in another country.

National control authorities should, whenever appropriate, exchange information on safety and other issues, within the normal legal constraints of confidentiality.

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

The health authorities should establish and maintain a competent national control authority with a defined organizational structure including, if relevant, a competent laboratory facility. The responsibilities, relationships, coordination, and legal status of employees should be specified in the light of their roles in a clearly defined decision-making process.

The authority can be either independent or part of the ministry of health. It is advisable to delegate decision-making responsibilities to those departments within the authority or laboratory with the necessary competence in the field of biologicals so as to facilitate the licensing/regulation process and ensure that it is carried out efficiently.

It is also recommended that the national control authority should make use of external expert advisers and advisory committees with appropriate expertise. Caution should be exercised when identifying such advisers to avoid conflicts of interest.

4.1 **Personnel** (see also 1, p. 34)

The personnel of the authority or laboratory 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.

All staff members of the authority should undergo suitable training and should therefore attend “hands-on” training courses covering both the technical and administrative aspects of licensing and control procedures.

4.2 Administration (see also 1, p. 34)

The national control authority should have established procedures for the receipt and review of manufacturers’ submissions and, if applicable, for testing samples provided in support of applications. When the review procedures, which include the evaluation of detailed reports, have been completed, a notice of approval (licence) or disapproval is sent by the authority to the manufacturer. It may also issue notices of suspension or revocation of approval. Consideration should be given to making appropriate legal expertise available in support of this activity. It is of the utmost importance that proprietary and commercial information is kept confidential.

4.3 Registration documents (see also 1, pp. 34–35)

The national control authorities should provide guidance on the information to be provided, the format to be used, and the acceptability of specific forms, and should maintain adequate filing and archiving facilities so that all submissions, evaluations, records and correspondence are available and kept up to date. A computer program for drug regulatory authorities can be obtained from WHO.¹

The national control authority should possess, or have access to, library facilities appropriate to its fields of activity. The documents available should include current national and international requirements for biological substances, and other relevant specifications and recommendations published by WHO or other official bodies.

4.4 Good manufacturing practices inspectorate

The national control authority should have access either to suitably qualified inspectors who are independent of manufacturers or to recent inspection reports from qualified inspectors. The purpose of inspections is to ensure that each manufacturer’s facilities and procedures comply with the principles of good manufacturing practice as described in national or WHO publications (1, Annex 1) and with the requirements and/or conditions for the approval of the product concerned. Guidelines are available on the conduct of inspections of manufacturers of drugs and biologicals (1, Annex 2; 2, Annex 2).

¹ Available on request, together with a user manual, from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

5. **Aspects of the licensing process**

5.1 **Establishing a registration system for existing medical (biological) products** (see also 3, p. 71)

Before any system of control can be effective, it is necessary to identify and catalogue all the products already sold or otherwise supplied on the domestic market, in both the public and the private sectors, that qualify for control. Guiding principles for national drug regulatory authorities that have yet to introduce comprehensive legal provisions on drug regulation have been published by WHO (3, Annex 6). An appointed day should be established after which no existing biological products may be lawfully distributed or supplied unless they have been notified to the authority, and no new product may be introduced until a request for a product and establishment licence have been granted by it.

The effective administration of the provisional registration procedure depends on:

- (a) the prior identification of all interested manufacturers and importers;
- (b) a precise definition of a notifiable biological product based primarily on the claims made for it on the label and the indications for use;
- (c) the issue of guidelines on the procedure to be followed.

Each notified product, as a minimum, must be identified by name, the names and full addresses of the manufacturer and of the responsible agent, if any, representing the manufacturer, the name and full address of an importing agent, a brief description of the manufacturing procedure including a declaration by the manufacturer that good manufacturing practices have been followed and a manufacturing flow chart, a description of the dosage form, its composition (including active and inactive ingredients (using International Nonproprietary Names where appropriate)), the therapeutic class, the indications, a copy of all labelling, including any package insert, a copy of any relevant certificates and warranties relating to the product or its components, and appropriate shipment conditions.

It is desirable for an updated compendium to be available containing information for the physician on approved products. This should distinguish those products given provisional approval from those given final approval (new product licences).

5.2 **Screening of provisionally registered products** (see also 3, pp. 71–72)

A rapid screening of all provisionally registered products should be undertaken at the earliest opportunity with a view to securing the withdrawal from the market of any product which, simply on the basis of a review of its ingredients and indications, is judged not to meet appropriate safety standards.

After this preliminary review, a set of longer-term priorities needs to be set for the definitive assessment of provisionally registered products. Consideration needs to be given to the resources required, in terms of both personnel and information. The review should be adapted to a proposed time-schedule, depending on which, additional information may be requested by the national control authority from provisionally registered companies, e.g. periodic safety updates or evidence of lack of efficacy.

5.3 **New product licences** (see also 3, pp. 73-74)

The licensing of a vaccine or other biological product requires the issue of licences for both the manufacturing establishment *and* the product. The approval or licensing of a manufacturing establishment for the production of biological products should be granted only if the manufacturer complies with the relevant international or equivalent national standards for good manufacturing practice.

A licence for a given biological product will be issued by the national control authority only when it is satisfied that the product is in conformity with the relevant national and/or international requirements, including the manufacturer's specifications, applicable to it.

The normal procedure for the issue of a product licence consists of the following three stages:

- (a) the manufacturing establishment and product licence applications are received from the manufacturer, screened for completeness, and then reviewed for evidence of compliance with good manufacturing practices and for safety, quality and efficacy by the authority's technical staff;
- (b) the authority may perform laboratory tests, review reports of or perform pre-licensing inspections, and seek the advice of external experts on specific technical questions when deciding whether or not to authorize the marketing of the product;
- (c) the formal administrative action to grant or refuse a licence is then taken by the designated authorized person.

The assessment of the product must be based on its safety, quality and efficacy when used as intended. However, the availability of the product may be dictated by national policy considerations, such as the national need for comparative efficacy and/or safety, or cost-effectiveness. Advice on basic or essential drugs is published periodically by WHO (4).

5.4 **Renewal and variation of licences** (see also 3, pp. 74-75)

The precise circumstances under which licence-holders are required to apply for a renewal or variation in a product licence differ from country to country and should be clearly defined by the national authority. In general, if a manufacturer wishes to vary the conditions of the approved

licence to any significant extent, the variations must be submitted to the authority for approval. Significant changes might include changes in aspects of the manufacturing procedures or the facility, or in the product specifications, dosage forms or labelling. The procedure for the renewal of licences is more variable. In many countries, reregistration, but not licence renewal, is required annually. In others, licences must be renewed every 5 or 7 years.

Licence-holders should be required, in all circumstances, to inform regulatory authorities immediately of unanticipated adverse effects that could possibly be associated with a licensed product and that might call for the licence to be made subject to certain restrictions or withdrawn (see section 8).

5.5 **Information on the manufacturing establishment**

(see also 1, pp. 35–36)

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

- Personnel, and in particular their qualifications and experience, organization and reporting relationships, training schedules and record-keeping systems.
- The location and construction of the building used for manufacture and control.
- The flow of raw materials, personnel and manufactured product through the facility.
- The animal facilities.
- Air, water and steam systems and power supply.
- Drainage and effluent systems.
- The segregation of operations.
- Lists of major equipment.
- Maintenance schedules for equipment and building services.
- Cleaning procedures, schedules and control measures.
- Quality-assurance and quality-control procedures.
- Storage and quarantine facilities, and procedures for raw materials, packaging materials, in-process and bulk materials, and 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 national control authority should review the availability of the

manufacturer's inspection reports. If a report is available from the country of origin, this should suffice. Alternatively, if no report is available, or no inspection has been performed, an inspection should be conducted before a licence is issued. The inspectors selected should be independent of the manufacturer and have sufficient expertise to conduct a meaningful review in accordance with the system of good manufacturing practices in use; this should include buildings, facilities, procedures, personnel and quality assurance.

5.6 **Information on the product** (see also 1, pp. 36–37)

The manufacturer should provide sufficient information to demonstrate the safety, quality and effectiveness of the product as manufactured and controlled in the establishment described above, and should refer for guidance to the national requirements or, if these are not available, the relevant technical requirements published by WHO. The submission should include the following, if appropriate:

- Information on the source materials (e.g. microorganisms, blood/plasma donations, cells/cell substrate, pollen), including their specifications and the tests used to demonstrate compliance with the specifications.
- A description of the cold-chain procedures employed.
- Information on the raw materials and packaging materials, including their specifications and the tests used to demonstrate compliance.
- Information on the methods of manufacture, including a description of the seed lot and cell-substrate systems used, together with in-process, bulk and final product specifications, and the tests employed to demonstrate compliance.
- The demonstration of the consistency of manufacture, for which the results of tests on a minimum of three satisfactory and consecutive production batches, ideally of different bulk lots, of a size corresponding to that contemplated for routine production, are normally required.
- Any proposal for the reprocessing of the product.
- The results of stability studies undertaken to justify the proposed validity period for the product under the indicated storage conditions.
- The labels and package inserts.
- The 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 national control authority should reflect any particular considerations relevant to the product. Chemical, physical and biological tests additional to those specified in national or international requirements may also be performed.

For imported products, results of testing may be obtained under the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see section 6).

6. **Alternative procedures for approval of imported products – the WHO Certification Scheme**

The national authorities of countries wishing to import biological products can 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, as summarized in this section, provides a suitable basis for the approval and release of imported products (2, Annex 3; 3, Annex 5). 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.

6.1 **Participating countries**

Each country participating in the Certification Scheme should communicate to WHO the name and address of the department of its national control authority dealing with biological products and, if appropriate, any significant reservations relating to its participation. WHO would then notify all other countries.

Exporting countries participating in the Certification Scheme should ensure that:

- the approval of biological products is subject to appropriate control testing by the national control authority to guarantee safety and efficacy, and that adequate facilities are available for such testing;
- the manufacturer complies with the requirements for good manufacturing practices and quality assurance of biological products as recommended by WHO, or with equivalent national standards;
- the national control authority conducts appropriate inspections including, for example, the examination of records and samples, so as to ensure that manufacturers comply with these requirements;
- the inspectors in the service of the authority possess the appropriate expertise.

Exporting countries participating in the Certification Scheme should, whenever possible, ensure that **International Nonproprietary Names** are used on certificates and for **labelling the biological product** (5).

6.2 Certification of products

Biological products exported under the Certification Scheme should be certified by the national control authority of the exporting country by means of certificates to be sent to the corresponding authority of the importing country. The importing country can 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 authority of the exporting country. Certificates would, however, be expected to state that:

- the product is approved for use within the exporting country or, if not, the reason for which approval has not been obtained;
- the manufacturing establishment in which the product is produced is inspected at suitable intervals to check that the manufacturer complies with the principles of good manufacturing practices and quality assurance (see *I*, Annex 2).

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

6.3 Requests for additional information

Additional information may be requested by the national control authority of the importing country from the corresponding authority of the exporting country. This information may be provided directly by the latter, or through the manufacturer, and may include:

- Information showing that the requirements for good manufacturing practices and quality assurance of biological products have been satisfied.
- Information on control tests performed on the product by the authority of the exporting country.
- 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 supplied with the product on packaging materials and package inserts and approved by the authority in the exporting country, 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 under the legislation of the importing country. Of concern, in particular, is information that will ensure that the quality of the product will not be adversely affected by the storage and shipment conditions. The consent of the manufacturer to the provision of such information should be obtained by the national control authority of the exporting country.

6.4 **Reporting of defects and adverse reactions**

Defects may occur in 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 national control authority of the importing country should notify the corresponding authority of the exporting country and provide the relevant data. Adverse reactions of unexpected severity or frequency should also be notified to the authority of the exporting country. Similarly, if the authority of the exporting country discovers quality defects or receives reports of unexpected adverse reactions, it should inform the corresponding authority of the importing country of the problem and any action taken. Guidance on the reporting of adverse drug reactions is contained in the report of a Working Group of the Council for International Organizations of Medical Sciences (CIOMS) (6, Annex 1).

7. **Authorization of clinical trials**

An authority may occasionally need to consider an application to conduct a clinical trial of an unapproved product for the prevention or treatment of a condition. To provide for this contingency, the registration system should include provision for the importation of the necessary materials, subject to appropriate controls. Such trials should take place only after formal clearance has been obtained from the competent registration authority and after assurances have been obtained that they will be conducted in conformity with the principles contained in the World Medical Assembly's Declaration of Helsinki, the good clinical practices guidelines of national authorities, and the CIOMS guidelines (7, Annex 1).

8. **Post-licensing monitoring**

(see also 1, pp. 39–40)

8.1 **Product release**

At the time a product is approved, the national control authority should decide what controls are to be applied to the release of batches of the product. This decision will be influenced by the nature of the product and the resources available for laboratory testing. Controls will usually be imposed on complex products, e.g. vaccines, and on those obtained by complex manufacturing procedures. The control system may involve the activities described below, and may be reviewed and revised once satisfactory and consistent production has been demonstrated:

The *testing of samples* of intermediate, bulk or final product should confirm compliance with the requirements and agreed specifications (see section 5). The nature and frequency of the tests to be carried out are decided by the national control authority.

The *evaluation of the manufacturer's protocols* for the manufacture and control of each batch will be undertaken by the national control authority. 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 authority 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.

8.2 Inspections

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

8.3 Post-licensing surveillance

The procedures described in sections 8.1 and 8.2 above do not preclude the need for a post-licensing sampling and surveillance system. Countries should establish a national system for the post-licensing surveillance of biological products. Clinicians and other health workers should be encouraged to report to national control authorities and manufacturers any unexpected adverse events occurring after the administration of biological products.

The mechanisms for reporting (e.g. standardized forms), the receiving body (e.g. the national control authority), the deadline for reporting (e.g. 48 hours), and the types of adverse events reportable need to be clearly defined by the authority and will depend on its structure and resources. The manufacturers and the authorities 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 the inspection of production and control facilities and local distribution channels. If an imported product is associated with adverse reactions, the manufacturer and, where appropriate, other national control authorities and WHO should be notified.

Guidance on the operation of a monitoring system for adverse reactions is provided in a CIOMS report (6). The national control authority or another government body may decide to perform epidemiological studies to obtain further information on the performance of products in actual use.

8.4 **Recall and revocation**

National control authorities should have a system for enforcing the recall of batches, revoking approvals, communicating such decisions to users, and ensuring that the authorities of other receiving countries importing the product are notified accordingly.

8.5 **Approval of manufacturing changes**

Any significant change in the manufacturing establishment, source materials, production process, quality-assurance procedures, product specifications or labelling is subject to the prior approval of the national control authority. Significant changes in the manufacturing process may require major modifications to the existing licence, and the submission of new lots of product to demonstrate consistency of manufacture and new clinical data.

8.6 **Approval of new indications**

National control authorities should require manufacturers to submit significant proposed changes in product indications for use for evaluation and approval. An authority may request additional clinical data if changes in the dosage regimen, including the dose, route, frequency or timing, are proposed.

9. **Powers of enforcement**

In order to assume its responsibilities, an authority must possess powers of enforcement backed by legal provisions for imposing penalties for offences such as misbranding, adulteration and the sale of counterfeit products. It should also have the power to order the suspension of lot release, seizure or recall when necessary to prevent the release of suspect lots or to ensure that suspected hazardous materials are withdrawn.

In establishing administrative decision-making mechanisms, the authority should not lose flexibility. In particular, it should make provision for:

- implementing decisions regarded as urgent in the interest of public safety;
- formal consultation (usually through representative bodies) with pharmaceutical companies and other interested parties, including pharmacists, doctors, nurses and patients.

The authority should publish a list of licensed products and sources at regular intervals.

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