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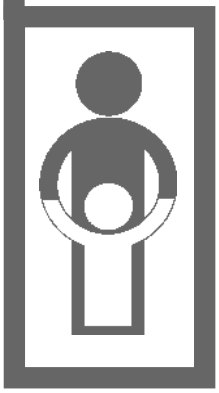
Regulation of vaccines: building on existing drug regulatory authorities



DEPARTMENT OF VACCINES AND OTHER BIOLOGICALS

World Health Organization
Geneva
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1. Introduction

WHO is often asked for advice by drug regulatory authorities (DRAs) and Ministry of Health officials to develop the capacity to regulate biological products, particularly vaccines. Although vaccines are generally included in the legal definition of pharmaceutical products, and thus would fall under the jurisdiction of DRAs, there are extra considerations that apply to their regulation and control.

These guidelines are based on analysis of activities to achieve this capacity in several countries. They have been jointly developed by the Department on Essential Drugs and Other Medicines (formerly Action Programme on Essential Drugs and the Division of Drug Management and Policies) and the Department of Vaccines and Other Biologicals (formerly the Global Programme for Vaccines and Immunization). They are based on existing WHO documents promulgated by WHO's three Expert Committees, namely, on Biological Standardization, on Specifications for Pharmaceutical Preparations, and on the Use of Essential Drugs (key references are listed in Annex 1). They are intended for countries that have functioning DRAs, but which are not yet engaged in regulation and control of vaccines and other biologicals.

Existing DRAs seeking to initiate or to strengthen systems for the effective regulation of biological products for use within their national borders and for those locally produced products intended for export may use these guidelines. The approach taken is to build new functions and co-ordination mechanisms onto those already existing in the DRA for all pharmaceutical products, not to build an entirely new authority. We have referred to a DRA that has added the functions and staff to effectively regulate vaccines as having a vaccine regulatory system. Some WHO documents also use the term National Control Authority (NCA) or National Regulatory Authority (NRA). None of these terminologies implies a separate structure for the regulation of biologicals.

2. Special principles and procedures applying to the regulation, control, and standardization of vaccines

Well-managed programmes of vaccination have brought about profound reductions in the impact of diseases in terms or morbidity and mortality in the majority of countries of the world. One major disease, smallpox, has been totally eradicated largely as a result of vaccination and another, poliomyelitis, is absent from large areas of the world and on target for eradication during the next few years, while the incidence of measles has been greatly reduced. Vaccines provide one of the most cost-effective of all public health interventions and are among the safest medicinal products.

These enormous achievements have been possible in part because effective and internationally agreed principles and procedures are in place to secure high levels of safety and efficacy and quality of vaccines. Vaccines differ from therapeutic medicines first because of the biological, and thus inherently variable, nature of the products themselves, the raw materials used in their production, and the biological methods used to test them. Thus special expertise and procedures are needed for their manufacture, control, and regulation. The use of appropriate WHO standard materials and reference preparations, where they exist, is fundamental to the standardization and control of vaccines.

New vaccines are being developed at a rapid pace and these vaccines will represent new and complex challenges for regulatory authorities as well as for vaccine manufacturers. Included in these developments in particular are conjugate vaccines such as those against meningococcal and pneumococcal disease. In addition, vaccines of fundamentally new design structure, such as DNA vaccines, are being evaluated.

Vaccines are unique in the fact that they are usually administered to very large numbers of healthy people, mostly infants, in national immunization programmes; thus safety and quality are paramount. Although vaccines have a key role in preventive medicine, recent history of their use has shown a general high level of safety compared to their benefit. In most cases minor adverse reactions may occur, but these do not challenge the risk-benefit advantage of vaccination. There are a number of potential and theoretical risks implicit in their use. They include in particular the presence of adventitious agents derived from source materials or introduced during manufacture or, in the case of live vaccines, the presence of virulent organisms (reversions of the vaccine virus). In these cases there may be a possible risk to the community at large in addition to vaccinees.

Because of these potential public health risks and the complexity and variability of the products, WHO recommends that the manufacturers' quality tests be reviewed with possible complementary testing by national regulatory authorities before release

of the product for use. A high level of special scientific expertise is required for the regulation and batch release testing of vaccines. In recent years, the licensing and quality control for manufacturers and national regulatory authorities alike has become even more complex by the development of vaccine formulations containing an increased number of immunogens. Each new vaccine combination needs to be carefully tested clinically and testing and specifications may vary for each specific product.

It is important that the standardization and control of vaccines by the national regulatory authority and the manufacturer are continually reviewed and modified so as to reflect the current state of science and technology, incorporating an improved understanding of quality and safety issues. Regulatory authorities must thus be proactive and maintain an acute awareness of scientific developments in the vaccine field.

3. Overview of drug regulatory authority functions

The overall objective of a drug regulatory authority (DRA) is to ensure that medicinal products (pharmaceuticals, biologicals including vaccines, blood products and other biologicals) are of acceptable quality, safety and efficacy, are manufactured and distributed in ways which ensure their quality until they reach the patient/consumer, and their commercial promotion is accurate.*

The main functions of a DRA are:

- registration (licensing) of products
- inspection and licensing of manufacturers
- inspection and licensing of distributors
- post-marketing surveillance
- regulation of claims that can be made for commercial promotion of products
- authorization of clinical trials.

A DRA can be effective only if it has:

- a legal basis for all its functions in legislation and regulations
- sufficient human and financial resources
- access to appropriate scientific expertise
- access to a quality control laboratory.

3.1 Marketing authorization (registration) of products

The function covers several activities:

- *Assessment of applications for marketing authorization (registration) of new products.*

  The DRA has three options:

  a) to make its own assessment of the documentation submitted regarding the quality, safety, efficacy and product information of the product based on the file submitted by the applicant. This should always be done for products manufactured in the country.

* An expanded discussion of these concepts is also available in the document "Effective drug regulation, what can countries do?" WHO/HTP/EDM/MAC(11)/99.6

b) to use assessment protocols from DRAs in other countries as a basis for making its own decision about applications.

c) to rely on decisions made by DRAs in other countries. For imported products, one approach might be through application of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Annex 1, reference 9). The DRA should then require that applicants submit a Certificate of a Pharmaceutical Product. This is a certificate issued by the DRA in the exporting country, giving information about whether the product is registered or not, the product information as approved by the DRA (see 3.5) and whether the manufacturer is inspected and conforms with WHO GMP guidelines.

- *Suspension or revocation of marketing authorization (registration)* if there is new information about the product (such as new serious adverse reactions), or it does not comply with the conditions for registration (e.g. does not conform with specifications for quality, changed composition), coupled with the ability to remove deficient products from the market.
- *Assessment of applications for changes (variations)* to registered products, such as changes in quality specifications, composition or manufacturing process or place.
- *Renewal of marketing authorization (registration)* at expiry of registration period. Many countries have a limited registration period, usually five years. At the end of the period, an application for renewal of registration has to be submitted with or without supplementary documentation on the product if the manufacturer or importer wants to continue to have the product on the market.

The DRA usually has a drug evaluation committee with appropriate scientific expertise, either an advisory or a decision-making body.

3.2 Inspection and licensing of manufacturers

A licence issued by the DRA should be required for production of any medicinal products. Manufacturers should be inspected before and regularly after licensing to ensure that their facilities and procedures comply with national or international GMP guidelines or other consonant requirements.

3.3 Inspection and licensing of distributors

All links in the distribution chain (importers, wholesalers and retailers/pharmacies) need a licence and should be inspected to make sure that they comply with the conditions designated in relevant regulations for obtaining and maintaining their license.

3.4 Post-marketing surveillance

- Surveillance of the safety of products on the market by monitoring adverse drug reactions
- Surveillance of the quality of products by analysing samples taken from manufacturers and the distribution chain, either randomly or because they are suspected of being substandard.

3.5 Regulating commercial promotion of products

When the DRA registers a product, it should also approve product information (data sheet), containing indications for use, contraindications, warnings etc. This is the basis for preparing prescribing and patient information. When there is a legal requirement that all commercial promotion of the product must be consistent with the approved product information, it serves as a means of regulating the advertising and promotion of the product.

3.6 Authorization of clinical trials

It should be a legal requirement that clinical trials can be initiated and conducted only after clearance/approval by the DRA and in accordance with the Helsinki declaration (see Annex 1 reference 6). The DRA should have a mandate to review protocols, and, where necessary to protect the safety of subjects, to require protocol revision and/or termination of the trial.

3.7 Regulatory capacity

A fully developed DRA has implemented all the functions in the table below. However, if there are no manufacturers in the country, the DRA does not need to do GMP inspections, unless it chooses to inspect manufacturers in other countries for imported products. It can also use assessments or decisions made by DRAs in other countries instead of doing full assessments of applications for registration.

	Product registration			Post marketing activities	GMP inspection	Distribution inspection	Regulate promotion	Authorize clinical trials
	Own assess-ment	Assess-ment other DRA	Decision other DRA					
Products produced in country	✓			✓	✓	✓	✓	✓
Imported products	✓	✓	✓	✓	(✓)	✓	✓	✓

Few developing countries have a fully developed regulatory authority. It is currently estimated that less than one in six WHO Member States have well-developed drug regulation. Those that do are usually industrialized countries. Of the remaining Member States, about three in six have varying levels of development and operational capacity. The remaining two in six either have no drug regulatory authority in place or a very limited capacity that hardly functions.

4. What are the essential features of a regulatory system for vaccines?

The discussion below has been specifically developed considering the regulation of vaccines and other biologicals. Taking into account the inherent variability of these products due to the biological nature of their starting materials, their manufacturing processes, and their test methods, WHO has identified six essential control functions to be undertaken by an effective vaccine regulatory system (NRA or NCA). These are:

- A published set of clear requirements for licensing (of products and manufacturers)
- Surveillance of vaccine field performance (safety and efficacy)
- System of lot release
- Use of laboratory when needed
- Regular inspections of manufacturers for GMP compliance
- Evaluation of clinical performance through authorized clinical trials

It will also be important for national regulatory authorities to have strong research programmes to enable them to keep up with new developments in the field of vaccines. Finally, because of the special biological nature of vaccines, it is important that all steps of the distribution and storage be well supervised, down to the end user. In many countries, this is not the responsibility of the national regulatory authority; where it is, this task should be well implemented.

It should be noted that all references to the vaccine regulatory system within this text do not imply that there is a separate regulatory structure dedicated to vaccines. Rather, the terminology refers to the group or groups which may already exist to assure the implementation of the six functions listed above for the regulation of vaccines.

The degree of implementation of these functions will vary depending upon the source of the product. The following chart illustrates the variation in the functions of DRAs to regulate vaccines in countries using different mechanisms to obtain their vaccines. As WHO has set in place procedures to ensure that appropriate regulatory functions are being performed for products which have been found acceptable for purchase by United Nations agencies (see reference 12, Annex 1), countries receiving vaccines only through United Nations agency purchase (such as WHO or UNICEF), have a lesser responsibility in terms of the essential control functions (see reference 10, Annex 1, for a summary). For countries sourcing vaccines through production and direct procurement, greater responsibility for ensuring vaccine quality is needed:

- If the country is producing vaccines, all six functions should be performed.
- For countries which are importing vaccines, fewer functions need be ensured within the authority of the importing country, although it should ensure that the appropriate regulatory activities are being carried out in the country of manufacture.

Vaccine source	Licensing	Surveillance	Lot release	Lab access	GMP inspections	Clinical evaluation
UN agency	✓	✓				
Procure	✓	✓	✓	✓		
Produce	✓	✓	✓	✓	✓	✓

4.1 Terms of reference

The terms of reference of the DRA for the regulation of vaccines should be established by legislation and supplementary regulations and should provide the authority to:

- define scientific documentation and criteria on which licensing of vaccines for use in the country will be assessed
- issue, vary, suspend or withdraw licenses for vaccine and other biological products on the basis of quality, safety and efficacy
- continually oversee the quality of the vaccines by releasing each lot intended for use in the country, using the Summary Lot Production Protocol as the minimum basis for review
- monitor the impact of vaccines in use through a well functioning surveillance system for safety and efficacy (not always located within the NRA) which provides for the possibility of taking regulatory action if problems are detected.

4.2 Staff, resources and qualifications

The staff and size of the authority is dependent upon the functions that it should assure, the number and variety of products it controls and the extent to which it depends or relies on the activities of well functioning authorities in the countries manufacturing the vaccines it has licensed for use. The professional staff should have a thorough understanding of, and practical experience in, the different facets of the work. They should carry out their work according to clearly defined and published procedures. It is recommended that the vaccine regulatory system use the published WHO guidelines on vaccine production developed by the Expert Committee on Biological Standardization and published in the WHO Technical Report Series, as a point of departure.

4.3 Assessment of performance

In order to allow DRAs to assess their performance in the regulation of vaccines, WHO has started, at several in-country and inter-country meetings, to develop indicators for these functions based on country inputs on how to judge these functions. So far, the indicators have been refined by inputs from 38 countries. Use of the

indicators will allow the development of a percentage score which can show the acceptability of such a DRA vaccine regulatory system and indicate where strengthening is needed. The current list of proposed indicators for each of the six functions plus for the legislative status of the DRA itself is given below in Annex 3.

The indicators are being developed as a first priority for DRAs in countries where vaccines are produced, recognizing the oversight function of these authorities in guaranteeing the quality, safety, and efficacy of the products of their local producers. Countries which import vaccines or receive them through an external source such as a UN agency need to ensure that the producing country has a well-functioning vaccine regulatory system as well as to monitor field impact (safety and efficacy) of the vaccine under conditions of use in their own countries. The indicators will therefore be essential to importing countries when choosing a vaccine source.

4.4 Additional key functions for a vaccine regulatory system

The additional activities to handle the regulation and control of vaccines that a DRA should take on should be based very strongly on the pre-existing DRA structure. Some of the activities needed for vaccines will be essentially identical to those already being done for other pharmaceuticals, but with a requirement for specific expertise in vaccines, implying the need for new staff and/or expert committees well-trained in the special aspects of vaccines. These include the areas of assessing the documentation for marketing authorization, GMP inspections, and authorization and evaluation of clinical trials on vaccines. However, there are several functions which are either not generally performed for regulation of most pharmaceutical products, or which should use a different approach. These include lot release, post-marketing surveillance, and use of the laboratory (see below).

4.4.1 Those similar to functions required for pharmaceuticals, but requiring additional expertise

In the areas of authorizing products for marketing, GMP inspections, and clinical trials, guidelines already promulgated for pharmaceuticals regulation can be used (see Annex 1, References); however there will need to be expert input to reflect the particular characteristics of vaccines, including the specific requirements to protect the safety of individuals involved in production. This expert input should, at minimum, be reflected in the composition of expert committees which are responsible for providing advice on regulation of pharmaceutical products. In addition, existing national guidelines for GMP and for conduct of clinical trials should be supplemented to reflect these particular characteristics. For example, for evaluation of clinical trials, the characteristics of vaccines with respect to the need to guarantee the consistency of the product under clinical trials, the measurement of appropriate clinical outcomes, and the specific expertise needed to review the trial data should be addressed and may differ for vaccines. Finally, due care should be exercised to ensure that the characteristics of the product which will be proposed for licensing are the same as those of the product which will be tested in humans.

4.4.2 Lot release

Lot release is key to the control of vaccines and similar biologicals, which are inherently variable due to the biological nature of starting materials, manufacturing process, and test methods. Therefore, post-licensing monitoring for vaccines and other biologicals involves, in addition to the above, lot-by-lot release, as each lot can be considered unique. Lot release should be based, at minimum, on the review of Summary Lot Protocols which describe the production process in detail. WHO has provided, in each of the guidelines for production of the individual vaccines, model Summary Lot Protocols which can be used.

To put a lot release function in place, first, it should be included in the regulations or guidelines that cover regulation of these biological products. Next, a format for Summary Lot Protocols can be adopted or adapted. Finally, the responsibility for lot release authority should be confirmed. Generally this responsibility rests with the Head of the DRA, but it has been delegated to specifically designated individuals within the health authority in some countries.

4.4.3 Post-marketing surveillance

Surveillance by a national regulatory authority encompasses many activities. These include:

1) The periodic inspections performed to evaluate compliance of manufacturers with GMP and conformance with approved manufacturing processes.
2) The continual monitoring of the quality of vaccines through lot release programs and *ad hoc* assessment of samples collected in the field (less important when lot release is rigorously performed).
3) Review and evaluation of adverse reactions to be reported by health care providers.
4) Monitoring for effectiveness and efficacy of vaccine preventable diseases.
5) Some agencies may include evaluation of vaccine uptake.

Post-marketing surveillance for vaccine adverse reactions may differ from that for pharmaceutical products because of the nature of and target population for vaccines. Thus, rather than being given to sick individuals over an extended period of time in multiple doses, vaccines are given usually to healthy infants in one or a few doses. This means that associations supporting causality will be difficult to establish or rule out. It also means that adverse events, even those occurring coincidentally, following immunization, will more likely be suspected of being related to immunization. Lack of effect for vaccines can be addressed only through the disease surveillance programme, but will likely be reported in individual cases. Finally, for pharmaceuticals, adverse events may be reported by treating physicians, through the manufacturers and through designated reporting sites, such as hospitals. This reporting mechanism might not be completely appropriate for adverse events following immunization. It tends to be the responsibility of the immunization programmes, which will generally be notified through the health center personnel, to investigate reports of adverse events following immunization, to determine whether they are in fact related to a vaccine quality problem, and to pass them on to the DRA for regulatory action. (See reference 13 listed in Annex 1.)

Both active and passive surveillance systems are valuable. Intensive surveillance for both adverse events and disease is important especially after introduction of new vaccines. Immunization records are valuable along with laboratory confirmation of disease when indicated.

The co-operation of multiple public health agencies may be necessary to obtain the necessary information to which the DRA has access. The DRA may not have the responsibility or the expertise to conduct these activities by themselves but rely on more appropriate structures. Expert advisory groups to assist in evaluating information obtained from post-marketing studies may provide valuable advice to DRA. The ability of the authority to respond to information generated by such surveillance is key.

4.4.4 Role of the laboratory

The role of the laboratory in the control of vaccines deserves special mention. Historically, the laboratory was key to the lot-by-lot control of vaccines, as they sought to "test quality in" to the final product. Current concepts of vaccine regulation rely more on the ability of the authority to oversee the entire process, with the laboratory playing generally only a confirmatory role in testing of vaccines. However, a well-functioning National Control Laboratory for vaccines is a key resource to the vaccine regulatory system, as the staff have the expertise in vaccinology which can help in regulatory decisions, such as evaluation of marketing authorizations, review of clinical trial data, review of adverse reaction reports, and assistance with GMP inspections. If there is already a well-functioning Drug Control Laboratory, there will need to be some consideration as to how laboratory support for the vaccine regulatory functions will depend on use of that laboratory (developing the Drug Control Laboratory into a laboratory which can also serve as a National Control Laboratory for vaccines, establishment of a separate National Control Laboratory for vaccines, or contracting out laboratory services). In addition, the role of the laboratory in developing and validating new test methods needs to be considered. Because the development of such a resource is a long and expensive process, newly developing vaccine regulatory systems may choose to contract laboratory services on an as needed basis in the interim. Annex 4 provides some guidelines on how to do this.

5. What are the steps to take to proceed?

5.1 Establishing a Task Force

The first and critical step will be the designation of a Task Force or working group charged with implementing the analysis and planning steps which will lead to the functioning of the vaccine regulatory system. This group should be appointed by the Ministry of Health, should be part of or work very closely with the existing DRA, and should have the necessary authority as well as a small working budget to do its job. Annex 5 provides the Terms of Reference of such a Task Force.

5.2 Inventory and self-assessment

The first priority of the Task Force will be to inventory the functions already existing, first for pharmaceutical products, and then for biological products. The attached indicators will be useful for this purpose (Annexes 2 and 3). This assessment phase can be looked on as an opportunity to review and strengthen the functions of the DRA while determining how best to build on them to develop the vaccine regulatory system.

5.3 Determination of needs

Based on the gaps identified in the self-assessment, the Task Force should then determine exactly what will be needed, in terms of staff, training, technical inputs, financial resources, and facilities and equipment to address those needs. For example, some of the needs will be addressed by developing published regulations or guidelines. In some countries regulations may need endorsement from the government or even the legislative bodies: this, it should be recognized, will consume and resources. This process will also require staff time, perhaps technical and legal input from within or outside the country, printing and distribution costs. As a second example, the addition of a lot release function may entail significant costs in terms of staff. To determine the needs, it will be necessary to determine exactly how many lots of each type of vaccine from each manufacturer are likely to be released during a given period, to estimate the length of time and resources needed to release each lot, and to plan for acquisition of these resources.

5.4 Developing a plan

The most important output of the Task Force will be the plan for developing the ability to regulate vaccines. The plan will be the blueprint for implementation. It should include at minimum the mission of the DRA with respect to vaccines, its key policies and strategies (to be formalized in the guidelines or regulations), the

identified gaps and needs, and the activities to be undertaken to fill these. The plan should include, for each activity, the time frame, the financing needed and its probable source, the individual(s) responsible for its implementation, and the indicators of successful implementation. An important component of this institutional development plan will be the training plan, which outlines what training activities and/or outside technical support are needed, what are the priority areas for training, who will be trained and where (if that is known), and how that training will be used to strengthen the regulation of vaccines.

5.5 Implementation

Implementation of the plan can then be done according to the timelines established. The major barrier to effective implementation of a plan is generally the failure to have high level political commitment to its implementation, so this would need to be assured as the first step. With commitment goes funding.

5.6 Monitoring and follow-up

The role of the Task Force may cease once the plan is developed and implementation is begun. However, it will be necessary to ensure that there is a monitoring mechanism built into the plan, and it would be useful to institutionalize the Task Force in some way to continue this role. Beyond the scope of this document but important for countries to consider, is an independent body responsible for recommending priorities for the immunization programme. The NRA may provide important information for such a body.

The steps for NRA development are summarized in Annex 6.

Annex 1:
References

Publications of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

Thirty-first Report, WHO Technical Report Series, No. 790, 1990

1. Annex 6. Guiding principles for small national drug regulatory authorities

Thirty-second Report, WHO Technical Report Series, No. 823, 1992

2. Annex 1. Good manufacturing practices for pharmaceutical products

Thirty-third Report, WHO Technical Report Series, No. 834, 1993

3. Annex 3. Good manufacturing practices for biological products (see ref 7)

Thirty-fourth Report, WHO Technical Report Series, No. 863, 1996

4. Annex 10. Guidelines on the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce
5. Annex 12. Guidelines on import procedures for pharmaceutical products

Publications of the WHO Expert Committee on the Use of Essential Drugs

Sixth Report, WHO Technical Report Series, No. 850, 1995

6. Annex 3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products

Publications of the WHO Expert Committee on Biological Standardization

Forty-second Report, WHO Technical Report Series, No. 822, 1992

7. Annex 1. Good manufacturing practices for biological products
8. Annex 2. Guidelines for national authorities on quality assurance for biological products

Forty-fifth Report, WHO Technical Report Series, No. 858, 1995

9. Annex 1. Regulation and licensing of biological products in countries with newly developing regulatory authorities

Publications of the WHO's Immunization Programme (Department of Vaccines and Other Biologicals)

10. National Control Authority, Guidelines for Assessment of Vaccine Quality in Non-producing Countries, WHO/VSQ/95.1
11. Guide for inspection of manufacturers of biological products, WHO/VSQ/97.03
12. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, WHO/VSQ/97.06
13. Surveillance of adverse events following immunization (AEFI) - Field guide for managers of immunization programmes, WHO/EPI/TRAM/93.02 Rev.1

Annex 2:
Indicators for self-assessment of drug regulatory capacity in functions relevant to regulation of vaccines

Legislation

- Does the country have drug legislation?
- Does the legislation have provisions for:
  - establishing a drug regulatory authority
  - issuing marketing authorizations (registration of products)
  - controlling clinical trials
  - analysis of products by a government or other independent laboratory?
  - product recall
  - licensing and inspection of:
    - manufacturers
    - importers
    - wholesalers
    - retailers/pharmacies
    - health care facility dispensaries?
- Are there sanctions for violation of drug legislation?

Drug regulatory authority (DRA)

- Is the DRA organized as:
  - an independent agency reporting to the Minister of Health
  - part of the Ministry of Health
  - are all DRA functions in the same organizational unit (e.g. not divided between different ministries or different departments in the Ministry of Health)?
- Are drug regulatory responsibilities separate from drug manufacturing responsibilities?
- What is the number of staff in the authority?
- Does the authority have committees with outside experts to support its activities?

Marketing authorizations (registration of products)

- Are there formal procedures and guidelines for marketing authorizations?
- For how long is a marketing authorization valid?
- Are marketing authorizations required for products
  - made by national manufacturers
  - procured by the public sector
  - imported by the private sector
- Is assessment of applications for marketing authorization based on
  - DRA assessment of documentation for quality, safety and efficacy
  - Assessment protocols from DRAs in other countries
  - Certificates from DRAs in other countries, based for example on the WHO Certification Scheme
- What is the number of products with a marketing authorization out of the total number of products in the country?

Clinical trials

- Is the DRA responsible for controlling clinical trials carried out in the country?
- If no, who is responsible for controlling clinical trials?
- Are there guidelines for clinical trials?
- How many clinical trials were carried out in the country during the last year?

Quality control

- Is there a government or other independent drug quality control laboratory in the country?
- Does the laboratory test
  - Non-biologicals
  - Biologicals?
- How many samples were tested during the last year out of total number of samples submitted/collected?
- How many samples failed out of total number of samples tested?

Post-marketing surveillance

- Does a system exist for surveillance and reporting of quality, safety, and efficacy?
- How many reports were received last year about
  - quality
  - safety
  - efficacy?

- How many products were recalled during the last year in relation to:
  - quality
  - safety
  - efficacy?

Licensing and inspection of manufacturers

- Is a licence required for drug manufacturing?
- Are there written GMP guidelines?
- How many inspectors trained in GMP inspections are there?
- How many licensed manufacturers where inspected last year out of the total number of licensed manufacturers?
- How many manufacturers comply with GMP requirements out of total number of manufacturers?

Annex 3:
Indicators for status of the vaccine regulatory system and six control functions

System to regulate vaccines*°

- Statutory basis for establishment of vaccine regulatory system and enforcement power*°
- Lines of authority which reflect the independence of the regulatory authority from manufacturer
- If there is recognition of other regulatory authorities, criteria are established *°
- Recall system*°
- Mechanism to confirm the destruction of lots and system to document that this has been done*°
- Appropriate expertise of staff*°
- Institutional development plan*°

Licensing process*°

- Evaluation of both facilities and products for licensing*
- Single standard of evaluation for imported and locally produced vaccines
- Written guidelines for submission of the file*°
- Written guidelines for GMP assessment *
- Established procedure for review of license application*
- Criteria for departures from the normal review process*
- Written guidelines for variance to license*
- Criteria for the selection and use of expert committees *
- Appropriate consultation between manufacturers and DRA prior to submission
- List of licensed products and manufacturers*°

Indicators: Surveillance of vaccine field performance*°

- Written guidelines and access to information from a system for the detection and investigation of adverse events following immunization*°
- Clarification of the nature of adverse events which should be reported*°
- Consideration of epidemiological data in accessing vaccine performance*°
- Routine system for regular review of safety and efficacy for regulatory action*°
- Provision for post-marketing monitoring in license (Phase IV)*

Indicators: Lot release*

- Based at minimum on protocol review (obligatory need for summary lot protocol as part of specification for procurement) and lot release certificate from the NRA of the country of origin*
- Written procedure and criteria for the lot release process (checklist, sampling. guidelines)*
- Access to product file, national control laboratory report (if applicable) and to inspection reports and complaints in case of problems *
- Records kept of lot release data for analysis of consistency of quality, and continual review and scientific dialog with manufacturers on issues of quality test results*
- Written criteria for exemption from lot release.*

Indicators: Evaluation of testing laboratory*

- Commitment to a laboratory quality system from management*
- Designation of a Quality Manager*
- Existence of a Quality Manual*
- Documentation of procedures in place (including document control, SOPs, study plans for control of specific products, retest policy)*
- Equipment documentation in place (including commissioning records, operation manuals and logs, calibration and maintenance schedules, validation protocols)*
- Staff training plan developed and implemented*
- Existence of an audit and review system*
- Validation procedures in place for all tests*
- Existence of a laboratory safety programme*
- Appropriate use, calibration and maintenance of standards and reference reagents*
- Monitoring and analysis of laboratory data trends on a product by product basis and appropriate corrective action as required*
- Participation in proficiency testing schemes and collaborative studies*

Indicators: GMP inspections

- Written requirements or codes consistent with WHO GMP requirements
- Provision for acceptance and issuance of documents certifying compliance with GMP
- Evidence of enforcement of GMP in production facilities
- Written plan for inspection procedures
- Appropriate qualifications for inspectors
- Inspections at regular, appropriate intervals
- Defined actions following inspection
- Independence of NRA inspectors from the manufacturer being inspected
- Expertise of the inspection team appropriate to the task
- Established procedure to monitor inspection process

Indicators: Clinical evaluation of safety and efficacy

- Policy of GMP, GLP, GCP, ethical oversight of trials
- Written guidelines for the conditions under which clinical trials will be needed: consideration given to the application of clinical data to the local use of vaccines
- Published guidelines on the format for submission of clinical data
- Access to expertise in epidemiology and statistics to advise on set up of and analysis of trials
- Access to experts in the product being tested (including experts in test methods)

° Indicators appropriate for countries sourcing vaccines through UN agencies.

* Indicators appropriate for countries procuring vaccines directly.

Annex 4:
Guidelines for contracting for laboratory support for regulation of vaccines

Introduction

WHO is often asked how countries which are procuring vaccines and which may need the assistance of qualified laboratories can assure access to those laboratories. Because laboratory testing of vaccines and other immunobiological products is complex, and needs meticulous standardization and controls, most diagnostic or research laboratories can neither perform these tests nor interpret the test results. To effectively control biological products, it is important for the testing laboratory to have:

- the necessary rigor when performing strictly standardized and validated tests,
- skills, expertise, reagents, and equipment appropriate to the test methods to be used, and
- the capacity to perform the tests at sufficient frequency to ensure reliability of the data and validation of reagents and the testing process.

Even some countries with well-functioning National Control Laboratories (NCL) for immunobiologicals may choose to find another laboratory to do certain tests which they perform infrequently.

This document is thus designed for countries whose DRAs need to contract for the use of an independent laboratory, either within or outside of the country, to complement the established mechanisms for control of vaccines.

Development of a laboratory

Examples of instances where laboratory testing may be needed include:

- the determination of whether or not a product proposed for licensing meets the specifications described in the license application;
- to ensure the identity of the product and compliance with relevant final lot characteristics as part of lot release;
- in case of a suspected break in the cold chain during the transport of the product from the manufacturer to the field;
- in the case of a reported complaint.

The activities of an NCL are as follows:

- Laboratory testing
- Advice on clinical trials
- Protocol review
- Developing laboratory tests
- Basic research
- Review of post-marketing surveillance data
- Input into licensing decisions
- Assistance with inspections
- Distributing references.

The NCL may be an entity separate from the DRA, or it may be part of it. Although the NCL will play a major role in the licensing and control functions for vaccines, the complexity of the functions to be performed dictate that many countries will not be able to establish a competent NCL immediately. Moreover, the standard of laboratory testing required for licensing, control and release of biological products is complex, expensive and demanding. The laboratory should be run according to the principles of Good Laboratory Practice, and the tests should be appropriately standardized, validated, and interpreted. For this reason, many countries, especially those which are importing vaccines, may choose to contract for services of accredited laboratories when laboratory functions are needed rather than establishing their own NCL.

Steps in selection of an independent laboratory

1) Draw up the terms of reference for the laboratory services desired

These should include:

- Tests to be performed
- Methodology and standardization of tests
- Capacity of laboratory (number of samples per time period)
- Turnaround time
- Price
- Reporting of results - are raw data only desired, or should the contracted laboratory interpret the test results?
- Provisions for maintenance of confidentiality.

2) Establish selection criteria

The selection criteria should be set out before the process of soliciting a laboratory is begun, so that the laboratory making a proposal will know what kind of information to provide in response to the request for proposals. Selection criteria which will be applied to all pre-qualified laboratories responding to the request for proposals could include:

- recommendations of other users of the laboratory or WHO,
- price of each of the tests to be undertaken, based on needed equipment, raw materials, and staff time,
- history of experience with the test or tests in question,
- sample shipment logistics (accessibility in terms of customs, flight schedules, special transport needs),
- responsiveness to needs as set out in the request for proposals, and
- results of previous evaluations.

Evaluations are covered in more detail below; however, some kind of standardized criteria for evaluation of laboratory services should be used. In some countries, there is a mechanism for accreditation of laboratories, which includes compliance with standard laboratory quality systems and ensures the reliability of the data generated. If such a mechanism exists, it should be used.

3) Assemble a list of possible qualified laboratories

Include, besides the name of the laboratory, the name of a contact person, the address, and telephone and fax numbers. Possible choices could include:

- the NCL of a well-functioning DRA with expertise in vaccine testing
- a proficiency-tested laboratory selected from among WHO's regional control networks (SIREVA, SEAR)
- any accredited laboratory for which proficiency in the desired test(s) has been demonstrated.

Guidance can be sought from the Department of Vaccines and Other Biologicals, WHO Geneva regarding proficiency testing, accreditation, and laboratory network members.

This "pre-qualification" step is essential to contracting out laboratory testing services.

4) Carry out the contracting process

The contracting process will normally be undertaken by the procurement entity responsible for purchasing vaccines and other biological products. The following points should be clarified before the process is started:

- What is the name of the body issuing the Request for Proposals?
- Who will sign the contract?
- Who will authorize payments?
- Who will make the payments?
- Is it the intention to contract for a specific series of tests or for a period of time during which a number of designated tests will be undertaken? If the contract is for a period of time the specific tests that will be required should be designated and prices requested.

The procurement entity should create a Request for Proposals in accordance with established procedures incorporating the detailed Terms of Reference created in Step 1 above. The Request for Proposals will be sent to the laboratories that have been evaluated by the DRA and found qualified to carry out the work to be undertaken. A minimum period of four weeks should be allowed for the laboratories invited to respond to the Request.

The evaluation of the proposals received may be carried out by a committee established for the purpose, or undertaken jointly by the procurement entity and the DRA. The evaluation should be based on criteria that are agreed when the Request for Proposals is issued and which establish the weight to be given to different factors. For example, the commercial merit of the proposal should be weighed in comparison with the technical competency of the laboratory offering the services.

The contract should be established with the laboratory making the most responsive offer for the services requested and at the best price.

5) Evaluation of the performance of the laboratory

The utility of the laboratory will depend on:

- the responsiveness of the laboratory to national needs for testing, including timeliness of reporting of results,
- ease of interpretation of results, if raw data are not requested, and
- reliability of data provided.

Good channels of communication between the vaccine regulatory authority and the contracted laboratory are essential so that any problems or discrepancies can be cleared up immediately. Systems for evaluating the data supplied should be established: for example, trends analysis could be done on the test values obtained for the standard or reference sample. It is desirable that the laboratory procedures and laboratory quality systems be reviewed on a regular basis through site visits by qualified inspectors. Proficiency test results and accreditation should also be reviewed regularly.

Annex 5:
Terms of reference of task force to develop regulation of vaccines

A Task Force should be appointed by the Minister of Health or the appropriate national official and invested with the authority to develop a plan for establishing a vaccine regulatory system, and to take that plan forward to implementation. Therefore, the Task Force should have the authority to make decisions on the structure and budget of such an authority, and should have a small working budget.

The proposed Terms of Reference of the Task Force are as follows:

1) To analyse the situation in the country *vis-à-vis* control of drugs and biological products, identifying strengths and weaknesses.

2) To gain consensus on what kind of system is necessary and advisory for regulation of vaccines, given the country situation.

3) To develop a step-wise plan to achieve the vision, including targets, milestones, and human and financial inputs needed, including the necessity for training and consultants.

4) To present this plan to the Minister of Health or appropriate high level officials for approval.

5) If the plan is approved, to put in place steps for its implementation.

The composition of such a Task Force is proposed as follows:

- Chairperson - an individual with sufficient knowledge and respect to be suitable for implementation of the plan
- Experts in fields important in the licensing, release and control of biological products, including, but not limited to, experts in vaccinology, immunology, pediatrics, animal science, and epidemiology
- Available to the Task Force as part of the study team should be the head of the immunization programme, the head of the disease surveillance system, the head of the DRA if one exists, and the person in charge of vaccine and pharmaceuticals procurement.

WHO can help in the following ways:

1) Discuss with the appropriate national authorities the needs and gaps.

2) Work with the Task Force and the larger study team on the vision for the future and in development of the plan.

3) Once the plan is approved, provide technical inputs within the context of the plan.

WHO does not have sufficient financial resources to provide these for implementation of the plan.

Annex 6:

Building upon a functioning drug regulatory authority

Function	Performance	Action
Licensing/ registration	Function exists, defined by legislation	Designate a focal point for biologicals regulation empowered to develop a Task Force on vaccine regulation. Task Force should include representatives with expertise in GMP (pharmacist training), epidemiology, biological laboratory and animal science, and vaccinology, and should plan for the development of vaccine regulatory functions, starting with licensing/registration
	Activity fully functional	In addition to the above, appoint experts in biologicals as members of Expert Advisory/Review Committee(s)
Post-marketing to surveillance of field impact	No systematic monitoring mechanisms exist in DRA	As a first step, monitoring of Adverse Events Following Immunization (AEFI) should be introduced in the immunization programme. An ability to detect and investigate reports of AEFI should be developed within the epidemiology and surveillance unit.
	Systematic monitoring mechanisms exist	Working with the epidemiology and surveillance unit, all AEFI reports should go to the DRA for review and regulatory action. This will require designation of a focal point within the DRA with some knowledge of epidemiology and of vaccinology.
Lot release	Key to vaccine regulation as opposed to pharmaceutical products (except antibiotics)	One or more experts with designated responsibilities in lot release should be recruited or designated, having training and experience in the manufacture and/or control of drugs or biologicals and specific expertise in microbiology. The terms of reference of their tasks will be developed by the Task Force above. Extra training in protocol review and lot release should be given.

continued/...

Annex 6: *continued/...*

Function	Performance	Action
Laboratory access	No DRA laboratory exists	The Task Force mentioned above should develop criteria indicating when laboratory testing is needed, as well as specifications for the laboratory tests and performance of the laboratory with a view to contracting out this function.
	A DRA exists and functions well, or a vaccine control laboratory, independent from the manufacturer, is available	The above criteria and specifications should be applied to the existing laboratory. Specific training where needed should be initiated in accordance with a step-wise plan.
Inspections for compliance with GMP	For countries procuring vaccines only	The Task Force mentioned above should develop criteria whereby the GMP certificate issued by the NRA of the country of manufacture will be recognized and include this in the prequalification process.
	For countries producing vaccines	The Task Force should ensure that a focal point be designated within the inspectorate to have special training in inspections of biologicals manufacturing facilities.
Clinical evaluation	No defined policy on clinical trials	As a first step, Task Force should review policies for pharmaceuticals and revise, with emphasis on defining when clinical trials will be used. This exercise should be consistent with GCP guidelines.
	DRA has defined policy on clinical trials	Above criteria should be refined for biologicals, including access to appropriate expertise, assurance of consistency of product to be used in Phase III trials recognizing the inherent variability of biological products, and outcome measures should trials be defined in terms of immune response.