Practical Guidance for Conducting a Review

(based on the WHO Data Collection Tool for the Review of Drug Regulatory Systems)
Authors

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Introduction

WHO's role in medicines regulation is based on its constitutional mandate and various World Health Assembly resolutions. These require WHO to support member states in their efforts to implement national medicines policies and programs, to ensure equity of access to essential medicines, medicines safety and quality, and the appropriate use of medicines. More specifically, WHO is requested to provide guidance and support on the setting up of efficient national medicines regulatory mechanisms, to ensure that available medicines are of good quality and to fight against counterfeited medicines.

TCM continues to assist countries on regulatory issues such as assessment of regulatory capacities and skills building. Greater focus is however being given to stimulating the country's commitment to effective regulation and to enable countries to determine themselves how their resources can be developed and applied most effectively.

TCM will work with countries in assessing national regulatory systems to monitor progress, identify gaps and develop strategies, in cooperation with national authorities, to improve medicines regulation. TCM will also help the country to introduce self-assessment mechanisms into their regulatory systems, thereby stimulating their own commitment to sustained improvement of their regulatory performance and to capacity building.

TCM will propose in both cases to the country to enter and follow its own Global Regulatory Support Process consisting of planning, assessing, reporting on identified gaps, providing recommendations, collaborating in the establishment of an institutional plan of action, providing support activities and follow-up.

Experience in developed countries has shown that development of regulatory capacities occurs in phases, over a long period of time. Factors such as the level of development of the pharmaceutical sector, the availability of trained human resources, infrastructure, the size and sophistication of the regulatory authority and financial resources, influence the regulatory functions that can be carried out.

Developing countries that are totally dependant on imported products and which have limited qualified human and other resources will thus need to start with limited priority activities, expanding them gradually as their pharmaceutical sector develops and resources become available.

Poor or inadequate regulation can lead to the prevalence of poor standard, counterfeit, harmful and ineffective drugs on national markets and in the international commerce. This can result in serious harm to the health of individual consumers and even to the health of a wider population. Therefore, countries must continuously strengthen key drug regulatory responsibilities so as to ensure the safety, quality and efficacy of drugs and the accuracy of product information.

Countries should assess their drug regulatory performance using indicators that focus on structures and inputs, processes and outcomes. They should identify any strengths and weaknesses, the reasons for them and consider alternative regulatory options, using the most appropriate and practical choices.

The WHO Data Collection Tool for the review of Drug regulatory Systems has been designed\(^1\) to help regulatory authorities perform such an assessment. More information on the design and development of this tool is provided in annex 12. This guidance provides technical advise on how to conduct this review.

Principles of Drug Regulation

The drug regulation structures that exist today (drug laws, drug regulatory agencies, drug evaluation boards, quality control (QC) laboratories, drug information centres, etc.) have evolved over time. Drug regulation is a public policy response to the perceived problems or needs of the society. Each country establishes its own regulatory framework and regulatory priorities according to existing and expected health risks and must adapt continuously to changing needs. Consequently, drug laws need to be updated to keep pace with the changes in the environment for which they apply.

One of the key concepts growing in extent is to combine post-authorization and pre-authorization activities in management of risks of pharmaceutical products and risk-minimization activities. This should also be considered by countries in the development and implementation of a comprehensive regulatory framework.

Drug laws, norms and standards

Legal structures form the foundation of drug regulation. Some drug laws traditionally omit or exempt certain areas of the pharmaceutical activity from their scope of control, resulting in a regulatory gap. To protect the public from harmful and dubious drugs and practices, drug laws should be comprehensive enough to cover all areas of pharmaceutical activity in the country.

While drug laws provide the basis for drug regulation, regulatory tools such as standards and guidelines equip drug regulatory authorities with the practical means of implementing the relevant laws. Standards and guidelines should be established in a written form for all drug regulatory functions. These tools should then be used to guide the regulatory practice, as well as being made publicly available to all the parties involved in order to bring transparency to the drug regulatory process.

Structure of Drug Regulatory Authorities

Drug regulation encompasses a variety of functions, such as licensing, inspection of manufacturing facilities and distribution channels, import and export controls, product assessment and registration, pharmacovigilance, Quality Control, control of drug promotion and advertising and control of drug clinical trials. Each of these functions targets a different aspect of the pharmaceutical activity and all of them should act in concert for an effective consumer protection.

In some countries, all functions related to drug regulation come under the jurisdiction of a single agency, which has the full authority in the command and control of these functions, as well as bearing the responsibility for their effectiveness. In other cases, drug regulatory functions are assigned to two or more agencies, at either the same or different levels of government. Two phenomena are found in the structural design of drug regulatory authorities which can present problems in regulatory effectiveness — fragmentation and uncoordinated delegation. Drug regulatory structures should thus be designed in such a way to provide for a central coordinating body with overall responsibility and accountability for all aspects of drug regulation for the entire country.

The drug regulatory authorities (DRA) in some countries are given non-regulatory functions such as drug manufacturing, procurement and/or delivery of services. Conflicts of interest in mandates and resource allocation can occur among these multiple functions and should be properly managed.

The DRA’s financial sustainability is a critical factor in the continued implementation of the various drug regulatory functions. The fees charged for regulatory services and government subvention are in general two different ways of financing the drug regulatory authorities.
The government should thus be fully committed to ensuring the financial sustainability of the drug regulation.

One of the major problems faced by the DRAs is the shortage of qualified personnel. A number of strategies can be considered in order to alleviate the shortage of human resources: better human resource planning; sharing and pooling of international resources on education and training, information and market surveillance; instituting incentives, prioritizing and streamlining work processes, job enlargement and job enrichment.

**Implementing drug regulation**

Several drug regulated areas, such as the informal sector, post-marketing surveillance and control of drug information receive relatively little attention in the implementation process. Counterfeit products, products of dubious quality and flawed information, especially exaggerated claims of efficacy are often found to be widespread in the informal sector. Unlicensed manufacturers, importers, wholesalers, retailers and even persons engaged in the pharmaceutical business pose difficult challenges to drug regulation. No matter how thoroughly the pre-marketing assessment is conducted, it is only one of the functions needed if the efficacy and, more importantly the safety of drugs are to be assured. Post-marketing surveillance functions, such as pharmacovigilance, QC testing and re-evaluation of registered products, should represent priority areas in drug regulation as well.

Drug information is distributed as widely as drug products themselves. Systems of regulating drug information include pre-approvals and self-regulation. However, monitoring of the accuracy and appropriateness of information is generally inadequate, and the effectiveness of existing systems of regulation is unknown.

**Monitoring and evaluation**

The regulatory process should be routinely and systematically monitored in order to identify the problems in the process and determine whether the activities actually carried out are consistent with the intended course of action. Several approaches such as self-reviews, supervisory body reviews and peer reviews may be used for assessing the DRA’s performance: These approaches can complement one another in appraising the DRA’s performance as well as assisting it to identify areas for possible improvements.

**Drug Regulatory Assessment Process**

The regulatory assessment should be understood as part of a global process of improvement. It is the preliminary step for an authority, a country or an organization to identify its gaps and weaknesses. The results should be the basis for a global perspective and plan for the improvement of its structure, capacities and efficiency.

WHO can take part in this process in providing expertise to perform this assessment as well as to provide the support for implementing the necessary corrective actions and to participate in the global increase of the level of quality of the organizations that deal with medical products.

The scope of the regulatory assessment could vary with respect to its objectives. A global assessment of the regulatory system will review all the organizations having responsibilities over all kinds of pharmaceutical products. Some assessments can focus on horizontal functions such as regulatory inspections for all categories of products or some vertical functions such as the review of the authorization, licensing and vigilance functions for a special category of products. Some assessments might also be Organization/structure-oriented in the review of all functions performed by a specific authority.

Each Regulatory assessment should be organized based on the following steps: planning, preparation, site visit, report, action plan and follow up. The different steps could vary depending on the kind of assessment performed (self-assessment or external assessment).
The process described below was developed by WHO/TCM for its own regulatory system assessments. It could be adapted to satisfy particular needs or organizations.

- **Expression of a need**

An assessment should always be based on an expressed need. This need can be formal for example an official request from a country to WHO, or informal such as in the case of a self-assessment. It could be internal for example following a program of quality management or external if a Ministry of Health asks for an assessment of one of its regulatory authorities. This is a major step because it will have an impact on the rest of the process: the definition of the scope, objectives, etc. Following this request, the first terms of reference of the assessment should be drafted (see annex 1).

- **Assessment team**

An assessment team comprising at least two assessors should be designated to undertake the assessment. The criteria for this selection should be based on the scope and the objectives of the assessment. For example the review of the whole regulatory system can be conducted by an assessor without specific qualification but if the review has to focus on a quality control laboratory, the assessment team can be composed of a pharmacist and an analyst. The recommended regulatory assessment competencies are as provided under annex 2. The assessors should belong to an independent group from outside the assessed organization and should not be involved in the processes reviewed. It is recommended that in case of recruitment of external experts, they be required to sign a confidentiality agreement (see annex 3) and a declaration of no conflict of interest (see annex 4).

The assessors should be selected with due regard to their education and past experiences in the assessed domain. If the assessment team is composed of several assessors, a team leader should be nominated as well as a "rapporteur" in charge of taking notes and keeping the documentation collected during the assessment. Usually a designated representative of the country or the assessed organization, accompanies the assessment team during its assessment.

If the organization requesting the assessment is not the assessed organization, the final team's composition should be agreed on between the two organizations.

- **Preparation**

The terms of reference of the assessment should be discussed, consolidated and agreed to between the assessment team and the requestor.

The duration of the review visit depends on the kind of assessment and should usually last from four to five working days. It might be longer depending on the scope of the assessment.

A precise date of the assessment should be planned in collaboration with all the involved parties.

The assessment team should begin by collecting the information on the regulatory authority. A request for documentation should be sent to the country/organization in advance to prepare the assessment (see table 1 in chapter 2. and annex 11). Useful information can be collected from previous/past assessments performed. The assessment team should begin by reviewing the collected information and completing the WHO Data Collection Tool. It is advisable to use electronic tools for collecting the information during the preparation, the assessment and reporting.

Based on this information, the team leader should prepare a draft agenda mentioning the different organizations, activities to be assessed (see annex 5) and the responsible person to be visited for each activity (see annex 6).
• **Visit**

Before embarking on the assessment and setting up any meeting, the assessment team should make a briefing to the senior level officials of the organization in most of the cases the Ministry of Health or the General Directorate in the case of a national regulatory authority.

• **Opening session**

Before the visit, an opening meeting should be organized to define the practical aspects of the assessment, to review the plan, to check the availability of personnel and to agree on the timetable of the assessment.

• **Performing the assessment**

During the visit, the assessment team should collect the needed information on the assessed organization following the order of the WHO Data Collection Tool. The assessors should mainly ask for documentation, review the records, interview the staff and make observations. Data should be collected and information should be registered directly in the tool. Gaps or weakness should be identified. Preliminary recommendations could be discussed with the members of the organization.

On certain matters or issues the assessor could also undertake interviews outside of the NRA's organization or the institution assessed for example representatives of stakeholders, to collate opinions or information on how the NRA is perceived or operates.

The assessors should review samples of records to check the implementation of the regulation, the guidance or the internal procedures of the organization.

The assessment team should be encouraged to organize at the end of each day a debriefing session with the personnel on the outcomes of the assessment in order to expose the main findings identified.

• **Closing session**

At the end of the visit, the assessment team should prepare a preliminary report containing the scope covered by the assessment, the strengths and gaps identified and the recommendations on corrective actions that should be undertaken.

The assessment team should then organise a closing session with the regulatory authority's staff that have been assessed. The estimated time frame for this closing session is half a day. During this closing session, the mains gaps should be presented and the recommendations proposed by the assessment team should be discussed. The assessment team and the organization's staff should be able to reach a common agreement on the recommendations. The preliminary assessment report should be amended taking into account the discussions with the regulatory authority's staff.

Following this discussion, a preliminary action plan should be developed by the assessment team and senior officials of the organization to specify how the recommendations could be implemented.

Situations can arise when the assessors do not share the same sentiments about a matter (gaps identified, recommendations of correctives actions, etc.). In such a case, the assessor should first go back to the documented evidence that cannot be challenged and this should then be recognized as pivotal. The assessor should always keep in mind that the content of the report is developed independently of the action plan which is a compromise between the assessment team and the assessed organization.
Follow-up

A draft report (see annex 7) containing the findings, gaps and recommendations should be made by the assessment team and should be submitted to the assessed organization timely for comments. The preliminary action plan of corrective actions (see annex 8) should be annexed to the draft report.

This draft report should be reviewed by the assessed organization which can send technical comments or propose some amendments to the report of the assessment team.

The report should be amended if necessary and finalized by the assessment team. The final report should then be submitted officially to the assessed organization and/or requestor, if different.

- **Following the regulatory assessment**

Following the final report, the assessed organization should prepare a final action plan of corrective actions. This action plan should take an operational format with the list of corrective actions that will be undertaken, the prospective deadlines or time limits for their completion with a clear mention of the responsibilities of the completion of these actions. The financial aspects or resources required can be added to this plan or mentioned separately.

Necessary actions should then be undertaken by the organization with or without the support of external interventions. The implementation of the action plan should be reviewed and documented under the format of an implementation plan (see annex 9).

**Different categories of assessments**

Following the different steps in the assessment process, different regulatory assessments can be performed for a certain period of time.

**Preliminary assessment**

A preliminary assessment can be organized to have a global overview of the system and to identify the main gaps or deficiencies.

**Follow-up assessment**

A follow-up assessment can be organized in a second intend after a preliminary assessment and after corrective actions have been implemented to check or to verify the effectiveness of the actions undertaken or to review the level of implementation.

Different regulatory assessments can be performed based on the scope for example specialized assessment can focused on;

- specific regulatory functions (Licensing, Inspection, Laboratory, Etc…) or
- specific products (marketing authorization decision making process for the pharmaceutical product X).

**Assessment duration**

The duration of an assessment of a regulatory system will vary form one type of assessment to another, the level of maturity of the Drug regulatory authority and also from the various functions that have to be assessed. The time allocated should be based on factors such as the size of the organization and the number of locations. Assessment duration will depend also on the audit frequency. Annex 2 from Guidance on the Application of ISO/IEC Guide 62 provides useful information on determination of the duration for assessment.
Assessment Methodology

The assessment methodology is based on several concepts which should be taken into account and followed.

An assessment should not be based on impressions, feelings or any subjective considerations. Furthermore it is important for the assessor to collect objective evidence of his observation. The laws or regulations published should be collected and any reference to internal procedures or Standard operating procedures/instructions should be quoted. These documents will be used afterwards as the basis for the proposed recommendations and will contribute to demonstrate the adequacy of the propositions to address any identified gaps.

Evidence may be collect by different means such as:

- Interviewing personnel.
- Reading documents.
- Reviewing manuals.
- Studying records.
- Reading reports.
- Scanning files.
- Analyzing data.
- Observing activities.
- Examining conditions.

The evidence collected through interviews should, whenever possible, be confirmed by more objective means. Investigational clues that point to possible deficiencies or gaps should be thoroughly investigated. The assessor should examine the collected evidence and document the gaps identified.

The assessor should not limit his activities to checking the presence or the absence of a document or a law. He should pursue to find the evidence on the implementation of the documents, procedures, guidance or laws.

For example, a law might have been published but no regulation has been adopted afterwards or the regulation has not been explained to other stakeholders through a guidance. As for the administrative procedures, the questioning methodology is the same; e.g. a procedure might have been established but not implemented. In such cases, the assessors should take samples of the records to identify the level of implementation of the procedure.

The regulatory assessment is a method to improve a regulatory system and it could be performed within the organization by internal personnel or by an external expert or a third party. It should not be understood as a means to enforce specific procedures or practices or to constrain people to act in a specific manner.
1. General information - Module 1

Objective:
To provide general and practical information on the assessment.

This module should be completed to provide general information on the country with the regulatory authority assessed.

1.1. Information on the country

The source of information (demographic, socio economics, statistics, etc.) can be found for a specific country in WHO statistics/Country indicators. It is recommended to collect data on the following topics:

- General indicators
  - Population (in thousands) total
  - Annual population growth rate (%)
  - Population in urban areas (%)
  - Gross national income per capita (international $)
  - Population below the poverty line (% of the population living on less than $1 a day)
  - Per capita GDP in international dollars

- Health Systems
  - Physicians (number) and Physicians (density per 1,000 population)
  - Nurses (number) and Nurses (density per 1,000 population)
  - Dentists (number) and Dentists (density per 1,000 population)
  - Pharmacists (number) and Pharmacists (density per 1,000 population)
  - Community health workers (number) and Community health workers (density per 1,000 population)

The assessor should keep in mind this set of basic information that should be help him during the assessment and for elaborating the action plan to provide adequate recommendations in relation to the country situation.

1.2. Information on the assessment

This chapter should also deal with the assessment performed, the purpose, the scope and the assessment team. This part should provide for a clear understanding of the focus of the assessment.
2. National Regulatory System - Module 2

2.1. Organization

Objective: To give an overview of the National regulatory system in the pharmaceutical products sector

The assessor should identify all the institutions, autonomous bodies, professional bodies, regulatory bodies, health institutions and any third party involved in the definition, implementation, compliance, enforcement and prosecution related to the regulation of pharmaceutical products. The level of intervention such as central level (MoH, National regulatory Authorities), state/province (Regional Regulatory Authority), district or community level (local authority) should be identified for each of the above-mentioned institutions.

Finally, the assessor should be able to identify the regulatory functions that each institution is responsible for and the categories of regulated products. This kind of mapping can be presented for a better understanding under a matrix (see table 1).

<table>
<thead>
<tr>
<th>Name of Country</th>
<th>Drugs</th>
<th>Herbal Medicines</th>
<th>Traditional medicines</th>
<th>Cosmetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers, distribution channel licensing</td>
<td>MoH</td>
<td>MoH</td>
<td>MoH</td>
<td></td>
</tr>
<tr>
<td>Marketing authorizations issuance</td>
<td>NRA</td>
<td>NRA</td>
<td>NRA</td>
<td></td>
</tr>
<tr>
<td>Performance of Regulatory Inspections</td>
<td>MoH</td>
<td>MoH</td>
<td>MoH</td>
<td></td>
</tr>
<tr>
<td>Quality control laboratory testing</td>
<td>NDCL</td>
<td>NDCL</td>
<td>NDCL</td>
<td></td>
</tr>
<tr>
<td>Safety monitoring of marketed products</td>
<td>National Vigilance center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial controls</td>
<td>National IRB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control of drug promotion</td>
<td>NRA</td>
<td>NRA</td>
<td>NRA</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Example of the Institutional involvement in the field of pharmaceutical products

At this stage, the assessor should begin to identify which organization is in charge of the coordination of all the institutions involved and understand by what means the regulated activities are being coordinated.

2.2. Legal basis for the establishment of the regulatory system

Objective: To get a general understanding of the legislative basis and legal terminology.

The term "legislation" refers to written laws, often referred to as Acts or Statutes, which are enacted by Parliament (the legislative arm of Government). The regulations are prepared under the authority of an Act, referred to as the “Enabling Act”.

The regulations are enacted by the body to whom the authority to make regulations has been delegated in the Enabling Act, such as the Governing Council or a minister, etc.

The guidelines are departmental documents that are used to interpret the legislation and/or a regulation. Although they may be derived from the legislation, they are often used to advise on how to comply with a regulation. The legal status of these guidelines can vary from one country to another but in any case they will not have the same level of empowerment as a legislative act. The country should establish a process to demonstrate that the applicable requirements concerning pharmaceutical products have been officially published and are publicly available to stakeholders that should implement them.

It is important for the assessor to understand how the different pieces of the legislation are drafted and which organizations/institutions are consulted during this process e.g. the public, the industry, the non-governmental organizations (NGOs) and other interested parties.

The assessor should identify the cases where the relevant legal provisions have been defined but the regulations have not been enacted and published, which implies legal uncertainty and potential misunderstanding or misinterpretation.

**Documented evidence to be studied**

- Organigram of the Ministry of Health
- Acts, Laws, Decrees or circulars establishing the regulatory system

**Reference**

How to Develop and Implement a National Drug Policy (Second Edition) (WHO; 2001; 96 pages)
3. National Regulatory Authority - Module 3

Objective:
To review the legal basis, the organization in place, the resources allocated and the good regulatory practices implemented by the organization.

Following the findings mentioned in the previous chapter, the assessor should review all the regulatory authorities that perform the regulated functions. In a first intent, the assessor should focus on the national regulatory authority if any. In some cases the assessor will have to assess regional or local authorities. Due to time, human or financial resource constraints, it may be necessary for the assessment team to decide to sample a limited number of regional or local authorities.

In the case of an assessment of multiple regulatory authorities, this module should be fulfilled for each regulatory authority assessed. In any case, if more than one institution is involved, the assessor should check if the legislation provides for clear coordination/linkage and avoids overlapping of the respective empowerments and also should look for any potential orphan areas.

3.1. Legal basis

The assessor should review the applicable legal requirements and if adequate, the regulations enacted to make the legislation precise.

The assessor should establish the terms of reference, functions, responsibilities, powers and structure of the Authority set out in the legislation. Furthermore he should establish the legal extent of the competencies of the Regulatory Authorities, and in particular if the NRA performs one of the following regulatory activities:

- the power to/or the delegation to authorize, suspend, amend or withdraw product market authorizations
- the power to/or the delegation to authorize the withdrawal/impose the withdrawal of unsafe products
- the power to/or the delegation to control the import and export activities of pharmaceutical products.
- the power to/or the delegation to register the pharmaceutical personnel
- the power to/or the delegation to license the facilities and to suspend or to withdraw these licenses.
- the power to/or the delegation to inspect the facilities where regulated activities on pharmaceutical products are performed.
- the power to/or the delegation to take the samples needed and to request for testing the product's samples
- the power to/or the delegation for authorization, suspension or stopping of clinical trials
- the responsibilities to participate in/or the delegation for the monitoring of the safety of marketed products.
- the power to/or the delegation for control of the promotion of pharmaceutical products.
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- the power to/or the delegation for monitoring the market and to ensure the implementation of the applicable requirements on the pharmaceutical products.
- the power to/or the delegation to charge and collect fees for regulatory services

The assessor should also identify the range of products to be monitored by the NRA: human/veterinary medicines, medical devices, herbal and traditional medicines, etc.

This legal scope can be slightly different from the activities that are really performed by the NRA. Significant differences should be pointed out.

For each of these regulatory activities see further module for continuing the assessment.

**Documented evidence to be studied**

- Acts, Laws, Decrees or circulars establishing the National Regulatory Authority,
- NRA's vision,
- NRA's missions.

### 3.2. Corporate Governance

In order to discharge its duties effectively, the NRA should function within an administrative organization that assures its independence of action. The NRA's management should be organized in order to take into account the following three components:

- the organization of the day to day work,
- the establishment of a prospective strategy,
- the evolution of the scientific environment.

The functions, roles and responsibilities of the different organs created within the NRA should be clearly defined and communication channels set in place.

**Documented evidence to be studied**

- Corporate plan, Strategic plan or Business plan

### 3.3. Institutional Development

Based on its Mission and Vision in line with Government policy, the NRA should establish a coherent development strategy which should be implemented and regularly updated. The NRA should elaborate the objectives regarding the regulatory functions performed and should monitor the achievement of such objectives using appropriate indicators which can be quantitative or qualitative, for example:

- Number of applications received (per year),
- Number of marketing authorizations granted (per year),
- Percentage of MAs granted within a timeframe/objective of 6 months/related to applications submitted

**Documented evidence to be studied**

- NRA's institutional plan
- NRA's objectives
- NRA's main indicators
3.4. **Organization and structure**

The assessor should identify the organization set in place to exert the regulatory functions; i.e. determine if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkage among the organizations particularly how the exchange of information is established and implemented.

3.5. **Quality Management System**

In this session the assessor should review the quality management system of the NRA for all its regulatory functions. Historically the Regulatory Inspectorate and the Quality control laboratory are the functions that have undergone quality assurance procedures before other functions. The assessor should find out whether the implementation of the Quality management system represents a global challenge for the NRA rather than building bridges between "islands" of partial quality systems.

The assessor should follow this questionnaire on the QMS which is applicable to the whole operational activities of the NRA. More specific questions are provided in the following chapters on the regulatory inspectorate functions (see chapter 5.3) and on the quality control laboratory functions (see chapter 16.3).

The number of staff employed in the quality management system activities should also be considered by the assessor (QI 3.5).

**Documented evidence to be studied**

- Quality Manager designation and job description
- Quality Manual,
- Procedure for documentation control (manual, procedures and records)
- Management review records,
- Quality policy and objectives,
- Quality Plan,
- Quality indicators (timeframe, reporting),
- List of internal procedures and forms,
- Procedure for planning, implementing internal audit and following up with corrections
- Audit reports and follow-ups
- Procedures for the investigation of non-compliance and records maintained,
- Procedures for dealing with complaints and records maintained.
- Procedure for initiation, decision and implementation of corrective and preventive actions and check efficiency and records

3.6. **Funding**

The assessor should identify if the NRA has a sustainable funding base. He should find out if the NRA is funded by the Government, by the fees collected for the services provided, by donor sources or for a mix. The availability of an adequate budget is essential to provide salaries that will attract personnel with the required training and experience, as well as the facilities and infrastructure needed. The assessor should determine if the NRA has the authority to charge, collect and utilize internally the funds it generated for regulatory services provided.
Documented evidence to be studied

- List of fees applicable for licensing, registration or authorization
- NRA’s budget
- Funding agreements

3.7. Management of human resource

The assessor should look at the NRA’s organization chart and review the duties, functions and responsibilities of the key technical and scientific personnel. This can be done by studying the job descriptions.

Some examples of key functions to review and interview are given hereunder:

- Director general/general manager/Head of DRA
- Heads of department/unit/section involved in regulatory functions
- Quality manager or representative
- Head of department/unit/section involved in supporting functions (IT, Logistics, Administration, Finance Etc…)

The assessor should not limit his investigation to the key personal only, but it is recommended to sample at least for each regulatory function the job description of each technical or scientific personnel involved in this functions and to review it.

In the following modules the assessor will have the opportunity to check if the functions described in the job description are the ones that are performed.

The development and training of the human resources needed should be planned with oversight from the organization. Particular attention should be paid to the definition of the minimum education, experience and training requirements for each category of staff. The organization of career planning and team building in the Governmental service and the evaluation of the need for external assistance, expertise or other kind of support services should also be prioritised.

The assessor should follow this general approach for the NRA by reviewing and completing the human resources sections of each regulatory function, including the education, experience and training of the staff employed to perform the regulatory activities. In this context, education refers to degrees, certification, and or licensing earned as a result of formal schooling or courses of study at an institution of higher learning (e.g. M.D:, Ph.D:, medical licenses). Training generally refers to short, focused programs on specific topics (e.g. two weeks training program on GMP). Experience includes a direct participation in the activities that provide additional expertise in a specific area.

The following indicators can be used by the assessors to assess the human resources processes and in particular the turn-over and the efficacy of the recruitment process:

- Total number of employees of the NRA (QI 3.1)
- Number of scientific staff (QI 3.2)
- Number of support staff (QI 3.3)
- Number of staff recruited (QI 3.6)
- Number of staff whose contracts are terminated in a defined period (QI 3.7)
- Number of staff recruited compared to total number of employees (QI 3.6/ QI 3.1)
- Number of staff whose contracts are terminated compared to number of staff recruited in a defined period (QI 3.7/ QI 3.6)
Documented evidence to be studied

- NRA’s organigram/organization charts
- Internal procedures for recruiting, training and qualifying staff and records
- Procedure for assessing the impact of training activities
- Procedure for assessing the competencies of the staff
- Code of conduct/code of ethics
- List of staff with their qualification
- Training plan
- List of trainings performed
- Job descriptions
- Curriculums Vitae
- Recruitment plan

3.8. Committees and external expertise

The assessor should identify if the NRA takes advantage of the expertise of external experts and/or if the NRA has set up committees of experts which intervene at a certain step of a regulatory process. The NRA can use the services of external experts or might have established one or several committees for example on marketing authorizations, on pharmacovigilance, on the control of promotion or on the control of clinical trials.

In the case of multiple advisory or technical committees, the questions of this chapter apply to each advisory committee identified.

The main issues are related to the independence of the different experts involved in the regulatory processes and to the management and prevention of potential conflicts of interest.

Documented evidence to be studied

- Internal procedures for selecting and designating external experts,
- Internal procedures for designating the members of the advisory committees,
- List of external experts,
- List of the advisory committees that intervene in a regulatory process
- List of the members of the advisory committees
- Composition of the various advisory committees
- Terms of reference of the various advisory committees

3.9. Transparency and confidentiality

The assessor should review the NRA's general practices and policies in dealing with transparency issues in all its procedures and outcomes. Above all the questioning should discuss the followings issues:

- The definition, publication and dissemination of the requirements for information to be submitted to the NRA in support of the various types of applications;

- The publication of the criteria used by the NRA and the procedures followed for decision-making on the applications;
- The publication of the NRA’s decisions (regular comprehensive lists of drugs registered, renewals and withdrawals) and of the information on which these decisions are based.
- The documentation and implementation of the appeal mechanism against the NRA’s decisions.
- The consultation or involvement of selected sectors of the civil society (such as NGOs, representatives of health professionals, industry, consumers and patients)
- The organization of regular scheduled meetings with key stakeholders and open days for the public as well as its representation in stakeholders meeting.

The assessor should also consider the answers given to the questions on availability of the information at the end of each module on the regulatory functions.

On this matter the assessor could also undertake interviews outside of the NRA’s; for example with the representatives of stakeholders to collect opinions or information on how the NRA is perceived or operates.

**Documented evidence to be studied**

- Acts, Laws, Decrees or circulars applicable to the NRA in this area
- Transparency policy
- Confidentiality policy
- Procedures to manage confidentiality
- Public availability of legal provisions, guidance and internal procedures on the website

### 3.10. Independence and impartiality

The assessor should find out if the NRA operates in an independent and impartial manner. The adequacy of procedures assuring independence and impartiality should be established for internal as well for as external experts.

Particular attention should be paid to the NRA’s advisory committees as regards the implementation of the documented procedure established for the management of such committees.

**Documented evidence to be studied**

- Acts, Laws, Decrees or circulars applicable to NRA in this area
- Code of conduct for internal staff, external experts and members of the advisory committees
- Internal procedures to manage the potential conflict of interest
- List of the Conflicts of interest declared
- Internal procedures to manage the advisory committees
- Minutes of advisory committees

### 3.11. Infrastructure

The assessor should ascertain if and how the NRA provides adequate buildings, work space, work environment and equipment to perform the assigned regulatory functions as well as support services in terms of transport and communication. The aspect related to Information management should not be discussed here and should be reviewed in chapter 3. 13.
3.12. Monitoring and accountability

The assessor should review the provision taken by the MoH or another organization to have oversight or to review how the NRA performs its activities. The assessor should check if one of the NRA's tasks is to prepare general and thematic reports, at periodic intervals, on the state of implementation of the laws. These reports should, inter alia, underline the deficiencies and weaknesses in the system and propose remedial action.

Documented evidence to be studied
- Reporting policy,
- Annual reports,
- Self-assessment reports

3.13. Information management systems

The assessor should review the NRA's information management system and in particular how the information is collected, entered into a computerized database and how queries are performed to retrieve desired information. The assessor should also find out if the NRA has established an integrated network of computers related to regulatory functions. Documented procedures should be in place to gather data, to use software applications or query tools. The NRA should have developed its own website or have made an arrangement to use the website of another organization/ministry.

The assessor should complete this general assessment by asking more specific questions after which he will have to review the availability of information for each of the regulatory functions.

The number of staff employed in the information management system should also be considered by the assessor (QI 3.4).

Documented evidence to be studied
- Number of pages on the NRA’s website or webpages
- Average time spent on the NRA’s website or webpages
- Number of computers available at the NRA
- Number of Information Technology staff
- List of the software applications used

3.14. Communication activities

The NRA is responsible for safeguarding public health by making sure that medicines work according to the intended purpose and are acceptably safe and should consider communication as a critical mission.
The assessor should review the NRA's communications strategy and how it plans to effectively communicate accurate and timely information about the benefits and risks of medicines to key stakeholders including the patients, public, healthcare professionals, researchers and industry.

Various communication channels can be used by the NRA to provide the interface with different stakeholders taking into consideration the different information needs.

Particular attention should be taken by the NRA with regards to the management of adverse events. The assessor should check if the NRA has prepared a plan to deal with critical events and to forward adequate information that can be urgently needed to protect the patient.

The success or effectiveness of this communications strategy should be periodically assessed by the NRA.

**Documented evidence to be studied**

- Communication strategy
- Web pages of NRAs website
- Plan for crisis
- Survey or study report on awareness of safety monitoring scheme, or public perception of NRA as source of information
- Meeting or conference programs and minutes

**Reference**

Regulatory Situation of Herbal Medicines - A Worldwide Review (WHO/TRM; 1998; 49 pages)


Effective Drug Regulation: What can countries do? (WHO/HTP/EDM/MAC(11)/99.6)

Effective drug regulation - A multicountry study (WHO; 2002; 47 pages)

WHO Policy Perspectives on Medicines N°7 - Effective medicines regulation: ensuring safety, efficacy and quality (November 2003, WHO Geneva)


Model guidelines on conflict of interest and model proforma for a signed statement on conflict of interest (Annex 4 - Marketing authorization of pharmaceutical products with special reference to multisource (generic) products - A manual for drug regulatory authority)

Measuring transparency in medicines registration, selection and procurement: Four country assessment studies (WHO/PSM/PAR/2006.7)

Pharmaceuticals and the Internet Drug Regulatory Authorities' Perspective - Joint NLN-WHI Workshop, 24-25 September 2001 (WHO; 2002; 80 pages)


Improving the quality and usefulness of drug regulatory authority websites (WHO Drug Information Vol. 15, No. 03 & 04, 2001 p.163 (WHO; 2000; 76 pages)
4. Marketing Authorization (MA) - Module 4

**Objectives:**

To assess the organization set in place to manage the registration process of medicinal products.

The assessor should review the legal framework within which the applications for marketing authorization of pharmaceutical products are submitted to the regulatory agency, the procedures for the assessment of these applications and the grant or refusal of marketing authorizations.

The NRA's application assessments should be based on defined criteria for safety, quality and efficacy of pharmaceutical products. The legislation should require the applicant to provide the information and data necessary for such an assessment. Furthermore the system of drug registration should include the review and approval of the information provided with the product such as data sheets and labels.

Different procedures can be used for the assessment of different categories of drugs (e.g. generic products or new chemical entities).

- For products indicated for standard uses and containing established ingredients, there is usually no need to re-evaluate the efficacy and safety of the active ingredients. Emphasis should be put on a review of other factors, for example the presentation, interchangeability (when indicated) and quality of the product, and the accuracy of the accompanying information.

- Considerably more extensive information should be required to support a marketing authorization application for a new drug substance, in order to provide for the assurance of quality, efficacy and safety. Particularly, detailed data should be required on chemistry, pharmacological properties, toxicological data, reproductive and teratological studies on animals, as well as clinical studies.

The following registration procedures may be established depending on the availability of technical expertise and resources:

- The NRA registers a drug, but no judgment is made on the registered products. The procedure does not involve checking whether the drug meets the basic safety, efficacy and quality criteria, but it provides a useful basis for developing additional control and improving the registration system.

- The NRA registers a drug following the decisions made available by the NRAs in other countries (a copy of an authorization, a certificate, etc…).

- The NRA registers a drug following the assessment reports or inspection reports made by the NRAs in other countries as a basis for decision-making on applications.

- The NRA registers a drug following its own assessment of the quality, safety and efficacy of the product on the basis of the information submitted by the applicant.

The assessor should review the NRA’s way of disseminating information regarding the efficacy and safety of new drugs in particular towards the patients or the general public. The information is usually disseminated through formularies, clinical guidelines and essential drugs lists.

To assure the availability of urgently needed critical medicines, specific legal instruments for such situations may be required. It is not always feasible to authorize needed medicinal products by standard registration process, frequently because of lack of interest of manufacturer to develop and submit data.
Existence of codified specific procedures serving for such purposes (e.g. compassionate use, exceptional authorization, conditional authorization, treatment programmes) should also be assessed.

4.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction of violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

4.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulations. Coherence with the WHO guidance should be checked and any differences should be identified.

4.3. Organization and structure

The assessor should identify the organization set in place to exert this regulatory function; if the function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkage among the organizations, how exchange of information is established and implemented.

4.4. Assessment procedures

The assessor should review the assessment procedures with respect to:

- the expected outcomes and achievements,
- their level of detail
- their adequacy with the training provided
- the controls applied to the process.

The assessors should pay particularly attention to review their coherence with applicable guidance, regulations and legislation.

Documented procedures for the assessment of the different parts of the application should consider the assessment of the followings issues:

- Pharmaceutical and chemical data/Quality part of the dossier
- Animal pharmacology and toxicology
- Clinical data on safety and efficacy
- Interchangeability and bioequivalence
- Labeling/packaging of the products
- Product information or Summary of Product Characteristics.

The assessor should identify the level of involvement of the inspectorate in the registration process in particular what kind of inspection is performed. The following indicators can be used to identify the level of surveillance by the NRA:

- Number of manufacturing facilities inspected (QI 13.4.1. and QI 13.5.1.) for pre-approval inspection for marketing authorization
The assessor should also review how information collected (pharmacovigilance) or submitted after the primary marketing authorization is given (variations) are managed in order to keep clear knowledge on the registered products continuously.

### 4.5. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indications to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received for a new drug (QI 4.4), for a generic product (QI 4.5), for renewals (QI 4.7) and for variations (QI 4.6), and if applicable include the number of periodic reviews based on percentage of total QI 4.2.
- Number of scientific staff involved (QI 4.1)
- Backlog (QI 4.9) or generated backlog (workload compared to the number of decisions taken) (QI 4.8)
- Average number of days spent by the NRA for decision-making on a new drug (QI 4.10), on a generic product (QI 4.11), on renewals (QI 4.13) and on variations (QI 4.12)

The assessor should review the adequacy of the competencies of internal evaluators and external experts as regards their qualifications in pharmacy, clinical pharmacology, medicine or a similar discipline, and their practical experience in at least one of these disciplines as well as in biopharmaceuticals.

The evaluators of product information and labelling should be qualified in pharmacy, clinical pharmacology, medicine or a similar discipline, and have practical experience in at least one of these disciplines.

Other competencies can be necessary for the assessment of specific parts of the application for example in the field of chemistry, microbiology, etc...

If external experts or an advisory/technical committee is involved in this process, the assessor should consider the questions under chapter 3.7 as applicable.

### 4.6. Records and outputs

The assessor should review how all the information collected during the licensing process are managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of internal procedures by the organization, the assessor should sample the records generated and check their contents.

The assessor should check also if outputs from this process (MA, variations, etc...) will become an input for the linked processes such as regulatory inspection, post marketing surveillance or drug promotion.

### 4.7. Availability of information

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.
Documented evidence to be studied

- Acts, Laws, Decrees
- Guidance published on the website
- Internal procedures, templates and records
- Assessment format and assessment reports
- Minutes of advisory committees’ or meetings of decision making chain
- Decision format
- Product information and Summary of product characteristics format
- Summary basis for decision format
- List of staff with their qualification
- List of external experts with their qualification
- List of authorized products/application registered
- List of applications refused or withdrawn
- List of applications pending,
- List and planning for periodic revision of the applications
- List of marketing authorization holders

Reference:


Model application form for new Marketing Authorization, Periodic Reviews and Variations, with notes to the applicant (Annex 6 - Marketing authorization of pharmaceutical products with special reference to multisource (generic) products - A manual for drug regulatory authority)

Model list of variations (changes) to pharmaceutical aspects of registered products which may be made without prior approval (Annex 10 - Marketing authorization of pharmaceutical products with special reference to multisource (generic) products - A manual for drug regulatory authority)

Detailed advice on evaluation of data by the Drug Regulatory Authority (Annex 7 - Marketing authorization of pharmaceutical products with special reference to multisource (generic) products - A manual for drug regulatory authority)


General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine (WHO MD; 2000; 80 pages)

Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (WHO/WPRO; 1993; 94 pages)

Guidelines for the regulatory assessment of medicinal products for use in self-medication (WHO/EDM/QSM/00.1; 2000; 28 pages)
5. Licensing of Manufacturers - Module 5

Objectives:

To assess the organization set in place to manage the licensing of manufacturers of finished products and active pharmaceutical ingredients.

The manufacturers are responsible for developing and manufacturing a good quality product and should adhere to the Good Manufacturing Practices (GMP). Furthermore, they should document their procedures and activities performed to ensure the quality of the product.

A mandatory system of licensing manufacturers, based on accomplishment of the current standards of GMP, is essential to ensure that all the products conform to acceptable standards of quality, safety, and efficacy. In addition, all premises and practices used to manufacture these products should comply with the applicable requirements to ensure a continued conformity to standards until the products are delivered to the end-user.

It is necessary to clearly define the various categories of license-holders, the content and format of licenses; details on the criteria on which license applications will be assessed and guidance available to interested parties on the content and format of license applications and on the circumstances in which an application for renewal, extension or variation of a license will be required.

The organizations engaged in the manufacture of pharmaceutical products should meet the prescribed criteria or requirements, regarding their facilities, personnel and practices, intended to assure the quality of the product up to the time of its usage/consumption.

5.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction against violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities).

5.2. Guidelines

The assessor should review the guidance published for all kinds of manufacturers (pharmaceutical products, investigational products, etc.) and find out, if the guidance covers the scope of the applicable legislation and regulations. The coherence with WHO guidance should be checked and any differences should be identified.

5.3. Organization and structure

The assessor should identify the organization set in place to exert this regulatory function; if the function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkage among the organizations, how the exchange of information is established and implemented.

5.4. Licensing assessment procedures

The assessor should review the procedures as regards their expected outcomes, their level of detail relative to the training provided and the controls applied to check the proper control of the described activities.
The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

The assessor should identify the level of involvement of the inspectorate in the licensing process in particular what kind of inspection is performed. The following indicators can be used to identify the level of surveillance by the DRA:

- Number of facilities inspected (QI 13.4 and QI 13.5) compared to the number of applications received (QI 5.4 and QI 5.5)
- Number of inspectors involved (QI 13.3)
- Average number of days spent on site (QI 13.6)

### 5.5. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received for a new premises (QI 5.4) and for modifications (QI 5.5),
- Number of scientific staff involved (QI 5.1)
- Backlog (QI 5.7) or generated backlog (workload compared to the number of decisions taken) (QI 5.6)
- Average number of days spent by the NRA to issue a decision (QI 5.8)

Note: Days calculated when all corrective action for the findings are closed

The assessor should review the adequacy of the competencies of the personnel involved in the licensing processes in particular as regards their qualification in Regulatory affairs and administrative procedures and their knowledge in manufacturing, GMP and drug quality control. This can be achieved by job experience, job training, etc…

The inspectors might be involved in the licensing process specifically for advising on the design or plan of production facilities, on the equipment qualification or process validation, etc.

### 5.6. Records and outputs

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of internal procedures by the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process (licenses, modifications) will become an input for the linked processes such as regulatory inspection.

### 5.7. Availability of information

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Guidance published
WHO Guidance for the assessment of drug regulatory systems

- Good manufacturing practices as adopted including the applicable supplementary guidance
- Internal procedures, templates and records for issuing licences
- Facility files on manufacturing sites
- List of staff with their qualification
- List of plants licensed, refused or withdrawn
- List of authorized persons responsible for the pharmaceutical activities

Reference:


Starting Materials


6. Licensing of importers, exporters, wholesalers and distributors - Module 6

Objective:

To assess the organization set in place to manage the licensing of importers, exporters, wholesalers and distributors

The company involved in the importation, exportation and distribution chain should ensure the proper storage of products, and their appropriate handling, packaging and distribution. They should also inform pharmacy or retail outlets about the correct handling and storage of drugs.

A mandatory system of licensing importing and exporting agents, wholesalers and distributors is essential to ensure that all products conform to acceptable standards of quality, safety and efficacy. In addition, all premises and practices used to store and distribute these products must comply with requirements to ensure continued conformity to standards until products are delivered to the end-user.

It is necessary to clearly define the various categories of license-holders, the content and format of licenses; details of the criteria on which license applications will be assessed and provide guidance to interested parties on the content and format of license applications and on the circumstances in which an application for renewal, extension or variation of a license will be required.

6.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

6.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulations. The coherence with WHO guidance should be checked and any differences should be identified.

6.3. Organization and structure

The assessor should identify the organization set in place to exert the regulatory functions; if the same functions is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkage among the organizations and how the exchange of information is established and implemented.

6.4. Licensing assessment procedures

The assessor should review the procedures as regards their expected outcomes, their level of detail in relation to the training provided and the measures applied to check the control of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.
The assessor should identify the level of involvement of the inspectorate in the licensing process in particular what kind of inspection is performed. The following indicators can be used to identify the level of surveillance by the NRA:

- Number of facilities inspected (QI 13.8) compared to number of applications received (QI 6.4 QI 6.5)
- Number of inspectors involved (QI 13.7)
- Average number of days spent on site (QI 13.10)

**6.5. Human and other resources**

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received for a new premises (QI 6.4) and for modifications (QI 6.5),
- Number of scientific staff involved (QI 6.1)
- Backlog (QI 6.7) or generated backlog (workload compared to the number of decisions taken) (QI 6.6)
- Average number of days spent by the NRA to issue a decision (QI 6.8)

The assessor should review the adequacy of the competencies of the personal involved in the licensing processes in particular as regards the following: qualification in Regulatory affairs and Administrative procedures and their knowledge of distribution, GDP, Drug quality control.

The inspectors may be involved in the process specifically in advising on the design or on the plan of the facilities, on the validation and control of environmental conditions.

**6.6. Records and outputs**

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures by the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes such as regulatory inspection.

**6.7. Availability of information**

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Good distribution practices
- Good Storage practices
- Other guidance published
- Internal procedures, templates and records for issuing licences
WHO Guidance for the assessment of drug regulatory systems

- Facility files
- List of staff with their qualification
- List of facilities licensed, refused or withdrawn
- List of authorized/qualified persons

Reference:


7. Licensing of pharmacies and retail outlets - Module 7

Objective:
To assess the organization set in place to manage the licensing of pharmacies and retail outlets

A mandatory system of licensing pharmacy and retail outlets is essential to ensure that all products conform to acceptable standards of quality, safety and efficacy.

It is necessary to define clearly the various categories of license-holders, the content and format of licenses; details on the criteria on which license applications will be assessed and guidance to interested parties on the content and format of license applications, and on the circumstances in which an application for renewal, extension or variation of a license will be required.

The organizations engaged in the sale and dispensing of licensed pharmaceutical products should meet the prescribed criteria or requirements, regarding their facilities, personnel and practices, intended to maintain the quality of the product up to the time of usage/consumption. They should also inform the patients about the correct handling and storage of drugs as well as provide for necessary information for their use.

7.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

7.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulation. Coherence with WHO guidance should be checked and any differences should be identified.

7.3. Organization and structure

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

7.4. Licensing assessment procedures

The assessor should review the procedures as regards their expected outcomes, their level of detail in relation with training provided and the controls applied to check the control of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

7.5. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative.
Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received for a new premises (QI 7.3) and for modifications (QI 7.4),
- Number of scientific staff involved (QI 7.1)
- Backlog (QI 7.6) or generated backlog (workload compared to the number of decisions taken) (QI 7.5)
- Average number of days spent by the NRA to issue a decision (QI 7.7)

The assessor should review the adequacy of the competencies of the personnel involved in the licensing processes in particular with respect to the following: qualification in Regulatory affairs and in Administrative procedures and their working experience in pharmacy or drug retail outlets of any kind.

The inspectors might be involved in the process specific in advising on the design of the facilities.

### 7.6. Records and outputs

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures by the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes such as regulatory inspection.

### 7.7. Availability of information

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information is maintained and updated on a regularly basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Good pharmacy or good dispensing practices guidance
- Other guidance published
- Internal procedures, templates and records for issuing licences
- Facility files
- List of staff with their qualification
- List of facilities licensed, refused or withdrawn
- List of authorized/qualified persons

**Reference:**

8. Registration of pharmacy personnel - Module 8

**Objective:**
To assess the organization set in place to manage the registration of the pharmacy personnel

8.1. Legal basis
The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

8.2. Pharmaceutical Practice Committee
The assessor should review if a Pharmaceutical Practice Committee has been established and if it is operational. The missions, responsibilities and internal procedures should be reviewed.

8.3. Disciplinary Committee
The assessor should review if a Disciplinary Committee has been established and if it operates. The missions, responsibilities and internal procedures should be reviewed.

8.4. Guidelines
The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulations.

8.5. Organization and structure
The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

8.6. Registration procedures
The assessor should review the procedures as regards their expected outcomes, their level of detail relevant to the training provided and the measures applied to check the control of the described activities.

The assessor should particularly review their coherence with applicable guidance, regulations and legislation.

8.7. Human and other resources
The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received (QI 8.3),
- Number of scientific staff involved (QI 8.1)
- Generated backlog (workload compared to the number of decisions taken (QI 8.4)
- Average number of days spent by the NRA to issue a decision (QI 8.5)

The assessor should review the adequacy of the competencies of the personnel involved in this registration processes in particular with respect to their qualification in regulatory affairs and in administrative procedures.

8.8. Records and outputs

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures by the organization, the assessor should sample the records generated and check their content. The assessor should check if output from this process will become an input for the linked processes such as regulatory inspection or licensing of premises.

8.9. Availability of information

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.

Documented evidence to be studied

- Acts, Laws, Decrees
- Code of conduct
- Guidance published
- Internal procedures, templates and records for issuing licences
- Pharmacists and technician files (records of the procedures, educational level, training, experience, …)
- List of staff with their qualification
- List of registered pharmacists and technicians, registrations refused or withdrawn
9. Post marketing surveillance and controls - Module 9

9.1. Import and export controls

Objective:

To assess the organization set in place to control import and export activities

To be fully effective, the marketing surveillance activities should be complemented by administrative procedures aimed at ensuring that pharmaceutical products are imported only if they have been authorized or have received an import licence before reaching the country. A consignment of imported pharmaceutical products should conform to all the particulars stated on the relevant import licence. All products that are imported should have been registered by the NRA or should have received a marketing authorisation. Import licenses as well as the controls that are applied on the imported products should be performed with reference to the market authorisation.

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

The assessor should review the guidance published for all kinds of stakeholders, and find out if the guidance covers the scope of the applicable legislation and regulations. Coherence with WHO guidance should be checked and any differences should be identified.

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received (QI 9.1), number of authorizations for importation granted (QI 9.2), number of certificates for export issued (QI 9.3)
- Number of scientific staff involved (QI 8.1)
- Average number of days spent by the NRA to issue these documents (QI 9.4)

The assessor should review the adequacy of the competencies of the personnel involved in the import and export processes in particular as regards their qualification in regulatory affairs, importation and exportation procedures.

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

The assessor should review the procedures as regards their expected outcomes their level of detail in relation to the training provided and the measures applied to check the performance of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.
While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes.

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Guidance published on Imports and exports controls
- Import control procedures, templates and records
- List of staff with their qualification
- List of products with importation and exportation authorization

**Reference**


**9.2. Market controls**

**Objective:**

To assess the organization set in place to survey the pharmaceutical products on the market

The emergence of counterfeited and other illicit products within domestic and international markets in recent years has imposed an extra dimension on the work of regulatory authorities and inspectors. It has also created the need for an enhanced collaboration between regulatory authorities, licence holders, customs officials and law enforcement authorities, as well as the need for greater vigilance by all persons involved in the manufacture, distribution and sale of medicinal products. Consideration should therefore be given to legal provisions that facilitate timely and efficient exchange of information among the concerned parties, both nationally and internationally, inter alia to counteract the illicit trade.

NRAs are advised to monitor the quality and safety of medicines to prevent harmful, substandard, and counterfeited medicines from reaching the public. Surveillance programs ensure that samples are randomly collected from the market and tested at scheduled intervals. Quality control plans and sampling strategies have to be developed on the basis of potential health risks identified or expected. Product labels and package inserts should be checked against those approved for registration. A system of receiving product complaints regarding quality should be instituted and the complaints should be investigated and documented.

Product quality can be surveyed by testing samples taken from manufacturers and from the distribution chain—either randomly or when grounds exist to suspect that a product may be substandard or counterfeit. Tests should be performed to ensure conformance to compendial requirements (e.g., British Pharmacopoeia, US Pharmacopoeia, International Pharmacopoeia, etc.) or to the manufacturer’s approved specifications where necessary.

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.
The legislation should provide authority to the NRA for sampling products on the market and for applying adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

The assessor should review the procedures as regards their expected outcomes, their level of detail and relevance to the training provided and the measures applied to check the performance of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

While reviewing the implementation of the internal procedures by the organization, the assessor should sample the records generated and check their content.

The following indicators can be used by the assessor to identify the level of control activities performed by the country:

- Number of products monitored (QI 9.5)
- Number of products detected as non-compliant (QI 9.6)
- Number of pharmaceutical products tested for market control (QI 14.5)
- Number of criminal prosecutions (QI 13.17) and legal sanctions (QI 13.18)

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regularly basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Guidance published on market controls
- Internal procedures, templates and records
- List of staff with their qualification
- List of monitoring program, actions implemented, in a reference period

**Reference**

Observations and recommendations on counterfeit drugs (Chap.8 - Quality assurance of pharmaceuticals - A compendium of guidelines and related materials - Volume1 - WHO; 1997; 238 pages)

Guidelines for the development of measures to combat counterfeit drugs (WHO/EDM/QSM/99.1)
9.3. Non-compliant products and recall procedures

**Objective:**

To assess the organization set in place to manage the pharmaceutical products of defective quality on the market.

The NRA should establish and implement a notification system in order to be properly informed of quality issues on pharmaceutical products already on the market.

The process to assess product complaints should take into consideration or envisage that the non-conformity observed can be due to non-compliant products.

Adequate provisions must exist to handle the recall of pharmaceutical products from the market and their destruction, requiring the manufacturers to recall unsafe, defective or inappropriately labeled products and, when necessary, to suspend the manufacture and commercialization where facilities or operations are found to be below standard as well as to cease unethical promotional activities.

Examples of possible actions to be taken include the suspension of a drug's marketing authorization, the recall of certain batches, warnings in national drug bulletins, or a separate warning sent out to a list of institutions and key persons dealing in/or prescribing pharmaceutical products.

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulations. Coherence with WHO guidance should be checked and any differences should be identified.

The assessor should review the procedures as regards their expected outcomes, their level of detail relative to the training provided and the measures applied to check the performance of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records generated and check their contents.

The following indicators can be used by the assessor to identify the levels of the control activities performed by the country:

- Number of complaints received (QI 9.7)
- Number of pharmaceutical products recalled (QI 9.8)
- Number of warnings or compliance notices issued by the NRA (QI 13.14)

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information is maintained and updated on a regular basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
• Guidance for manufacturers, importers exporters and distributors on how to handle/organize a recall, including the destruction of defective products.

• Internal procedures for handling quality defects (notifications of suspected quality defects, companies batch recall) and records

• List of staff with their qualifications

• Internal procedures for organizing a recall

• List of recalls performed
10. Control of drug promotion and advertising - Module 10

Objective:
To assess the organization set in place to control the promotion and the advertising activities of pharmaceutical products

A pharmaceutical is a chemical product plus its information. It is a very important task of the regulatory agency to ensure that drug information is unbiased, correct, updated and easily accessible to people prescribing pharmaceutical products, patients and consumers.

The regulations on the control of drug promotion and on the assurance of the quality of information provided with the pharmaceutical product are important for promoting rational use of medicines. The national drug policies should therefore include the necessary provisions for the regulation of promotional activities. The guiding principles should be the following: promotion should comply with national health policies and national regulations, furthermore it should meet voluntary standards where these exist. All promotions making claims should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste and based on information approved by the NRA.

Monitoring the quality of promotional activities needs adequate resources and a clear political commitment to enforce the relevant regulations. Possible sanctions include appropriate fines and published retractions of misleading claims in the media in which they were originally made.

10.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

Furthermore the assessor should review the range of products subjected to the control of promotion and the advertising activities: human, veterinary medicines, herbal medicines, etc.

10.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders, and find out if the guidance covers the scope of the applicable legislation and regulation. Coherence with WHO guidance should be checked and any differences should be identified.

10.3. Organization and structure

The assessor should identify the organization set in place to exert this regulatory function; if the function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

10.4. Internal procedures

The assessor should review the procedures as regards their expected outcomes, their level of detail and relevance to the training provided and the measures applied to check the performance of the described activities.
The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

10.5. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of applications received (QI 10.2), Number of promotion and advertisement documents monitored (QI 10.3)
  - Number of staff involved (QI 10.1)
- Generated backlog (workload compared to the number of decisions taken (QI 10.4)
- Average number of days spent by the NRA to issue a decision (QI 10.5)
- Number of documents found non compliant (QI 10.6)

The assessor should review the adequacy of the competencies of the personnel involved in the control processes in particular as regards their qualification in regulatory affairs and administrative procedures.

If external experts or an advisory/technical committee is involved in this regulatory process, the assessor should consider the questions of chapter 3.7 as applicable.

10.6. Records and outputs

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records emitted and check their content.

10.7. Availability of information

The assessor should review the information that is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information is maintained and updated on a regular basis.

Documented evidence to be studied

- Acts, Laws, Decrees
- Internal procedures and records
- List of staff with their qualifications
- List of authorized promotional and advertisement materials
- List of promotional and advertisement materials refused or withdrawn

Reference:

Drug promotion : what we know, what we have yet to learn (WHO/EDM/PAR/2004.3)
How to Develop a National Formulary Based on the WHO Model Formulary - A Practical Guide (WHO; 2004; 45 pages)

Guidelines for the Appropriate use of Herbal Medicines (WHO/WPRO; 1998; 88 pages)

11. Pharmacovigilance - Module 11

Objective:
To assess the organization set in place to collect, assess and take the necessary decision as regards the safety of pharmaceutical products

The aim of this module is to assess the monitoring of adverse drug reactions (ADR). A reporting system should be established to monitor medicine’s safety. The NRAs are advised to collect, evaluate and investigate the information on reported ADR and to take the appropriate decisions.

The scope and extent of the pharmacovigilance should be clearly defined in the legislation, regulations and guidance. An advisory committee should be established within the regulatory authority in charge of the monitoring to participate in the review of the ADR reports.

Countries should consider whether they have the capacity and the adequate resources to establish their own adverse reaction reporting mechanism, and the regulatory capacity to use the information gathered. Furthermore they should consider to implement reporting requirements that commensurate with their organization and envisage a scale up in the requirements in proportion to the improvement of their organization.

Networking with other international bodies and NRAs is a logical method for acquiring, sharing, and exchanging the relevant information on medicine safety and for basing a decision on which to take the appropriate action.

Awareness programs to promote pharmacovigilance among medical and health professionals should also be carried out by the DRA itself or by another organization under its control.

11.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

11.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulation. If different organizations take part, roles and responsibilities for each should be clearly mentioned. Coherence with WHO’s guidance should be checked and any differences should be identified.

11.3. Organization and structure

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.
The assessor can use the number of contact points (QI 11.3) within the country and the total number of ADR/ADE reported (QI 11.3, QI 11.4, and QI 11.5) to determine the level of involvement towards pharmacovigilance by referring to the health care systems indicators mentioned in module 1.

### 11.4. Internal procedures

The assessor should review the procedures with respect to their expected outcomes, their level of detail and adequacy relative to the training provided and the controls applied to check the performance of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

In the context of pharmacovigilance, the assessor should take particular attention to the delays and time frame taken by manufacturers, administrative, intermediate and central levels to transmit vigilance information, to investigate and to decide.

The assessor should identify the level of involvement of the inspectorate in the control of pharmacovigilance practices, in particular if inspections are performed. The following indicators can be used to identify the level of surveillance by the DRA:

- Number of facilities inspected on pharmacovigilance in the reference year (QI 13.14)
- Average number of days spent on site per facility inspected (QI 13.15)

### 11.5. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of ADR/ADE reported (QI 11.3, QI 11.4, and QI 11.5) and periodic reports reviewed (QI 11.6)
- Number of scientific staff involved (QI 11.1)
- Backlog (QI 11.8) or Generated backlog (workload compared to the number of decisions taken (QI 11.7)
- Number of investigations performed
- Number of warning letters/safety notices generated
- Average number of days spent by the NRA to make a decision (QI 11.9)

The assessor should review the adequacy of the competencies of the personnel involved in the monitoring processes in particular as regards the following areas:

- Experimental toxicology
- Animal studies
- In vitro testing
- Clinical pharmacology
- Pharmaco-epidemiology
- Drug utilization
- Statistics and Epidemiology
If external experts or an advisory/technical committee is involved in this regulatory process, the assessor should consider the questions of chapter 3.7 as applicable.

11.6. Records and outputs

The assessor should review how all the information collected during the reporting and assessment processes are managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records emitted and check their contents. The assessor should check if output from this process will become an input for the linked processes such as Marketing Authorization or regulatory inspection.

11.7. Availability of information

The assessor should review the information that is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regularly basis.

Documented evidence to be studied

- Acts, Laws, Decrees
- Internal procedures and records
- Initial and periodic ADR format for reporting
- Format of report to exchange information with other DRA and WHO
- List of staff with their qualification

Reference:

Safety of Medicines A guide to detecting and reporting adverse drug reactions (WHO/EDM/QSM/2002.2)

Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (UMC; 2000; 28 pages)

The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products (WHO; 2002; 52 pages)


WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems (WHO; 2004; 82 pages)
12. Clinical Trials - Module 12

Objective:
To assess the organization set in place to regulate the clinical trials

The aim of this module is to review how the regulatory authority is performing the control of clinical trials (CT) that are conducted on its territory. A NRA should consider the need for an application to conduct a clinical trial of an unregistered drug or a registered drug with new intended uses for example. To achieve this, a registration system should include the necessary provisions for the manufacture and importation of the materials needed, subject to the appropriate controls. Such trials should take place only after formal clearance has been obtained from the competent registration authority. Moreover, assurances should be obtained on the conformity of the CT conducted with the principles stated in the World Medical Association’s Declaration of Helsinki and the guidelines issued by the Council for International Organizations of Medical Sciences. Such trials should be carried out following good clinical practices and with the intervention of an ethical committee.

An advisory committee can be established within the regulatory authority to participate in the review of the CT applications.

Countries should consider whether they have the capacity and resources to establish their own CT registration mechanism, and the regulatory capacity to assess the information provided and to supervise the study conducted on their territory. Furthermore they should consider to ask in a first intend for notification requirements commensurate with their organization and envisage a scale up in the requirements towards a formal registration procedure in proportion to the improvement of their organization.

The assessor should review the processes applied by the DRA to authorize the various clinical studies and also check how the NRA organizes the monitoring of on-going clinical trials to check compliance with the conditions of authorization (approved protocol, investigators brochure, etc…).

12.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

12.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders, if the guidance covers the scope of the applicable legislation and regulation. If applicable the coherence with WHO’s guidance should be checked and any differences should be identified.

12.3. Ethical oversight

The assessor should be able to assess the extent of the controls that are applied by the NRA and to review the ethical oversight applied on the clinical trials.

The assessor should pay particularly attention to prevention of conflict of interest and ensuring that the confidentiality issues are taken into account in the management of the organisation.
The assessment team should have the opportunity to interview the chairman or representative members of IRB and/or IEC as well as to visit the premises.

12.4. Organization and structure

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations and how the exchange of information is established and implemented.

12.5. Assessment procedures

The assessor should review the procedures with regards to their expected outcomes, their level of detail and adequacy in relation to the training provided and the measures applied to check the performance of the described activities.

The assessor should particularly review their coherence with applicable guidance, regulations and legislation.

The assessor should identify the level of involvement of the inspectorate in the control of clinical trials in particular what kind of inspections are performed. The following indicators can be used to identify the level of surveillance by the DRA:

- Number of CTs inspected (QI 12.8) for GMP and GCP compared to the number of CT applications received (QI 12.2)
- Number of inspectors involved (QI 12.7)
- Average number of days spent on site (QI 12.9)

12.6. Human and other resources

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Workload for the functions performed with the following indicators: number of clinical trial applications received (QI 12.2) and number of applications for amendments received (QI 12.3)
- Number of staff involved in the control of clinical trials (QI 12.1)
- Backlog or generated backlog (workload compared to the number of decisions on clinical trial applications (QI 12.4)
- Average number of days spent by the NRA for decision-making (QI 12.5) and/or average number of days spent by the IRB/IEC for decision-making (QI 12.6)

The assessor should review the adequacy of the competencies of the personnel involved in the processes in particular the following qualifications:

- Biostatisticians,
- Clinical pharmacologist,
- Physician.

The assessors of CT applications should have the appropriate knowledge in the applicable laws and regulations, a broad knowledge of internationally accepted principles and practices for the conduct of clinical research within GCP, including the ethical requirements for the protection of human subjects involved in the research.
If external experts or an advisory/technical committee is involved in this regulatory process, the assessor should consider the questions of chapter 3.7 as applicable.

12.7. Records and outputs

The assessor should review how all the information collected during the approval process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records generated and check their contents.

12.8. Availability of the information

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regularly basis.

Documented evidence to be studied

- Acts, Laws, Decrees establishing the control of clinical trial
- Guideline
- Good Clinical Practices
- Good Laboratory Practices
- List of ethics committees
- List of the members of ethics committee
- Internal procedures
- Procedures to select and designate the members of the ethics committees
- Procedures to review a CT application/protocol by IEC/IRB
- Internal procedures, templates and records
- Internal procedures to deal with adverse drug reactions and records
- List of staff with their qualification
- List of clinical trials authorized, refused or withdrawn (per year)

Reference to be used

Handbook: Quality practices in basic biomedical research (ISBN 92 4 159445 4 120 p)
Handbook: Good laboratory practice (TDR/PRD/GLP/01.2 226 p)
Good laboratory practice: training manual (TRAINEE) (TDR/PRD/GLP/01.1B 141 p)
Good laboratory practice: training manual (TRAINER) (TDR/PRD/GLP/01.1A 302 p)
WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects
International Ethical Guidelines for Biomedical research involving Human Subjects (Geneva 2002: ISBN 92 9036 075 5)
Operational Guidelines for Ethics Committees That Review Biomedical Research TDR/PRD/ETHICS/2000.1
Surveying and evaluating ethical review practices 2002 22 pages TDR/PRD/ETHICS/2002.1

Operational guidance: Information needed to support clinical trials of herbal products (TDR/GEN/Guidance/05.1)

Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards (TDR/GEN/Guidelines/05.1)


Handbook for good clinical research practice (GCP) - guidance for implementation (WHO; 2005; 125 pages)

Workbook for Investigators (TDR/PRD/GCP/02.1b 272 p) - TDR 2002


13. Regulatory inspections and enforcement activities - Module 13

Objectives:

To assess the organization set in place to inspect, monitor compliance with the applicable requirements and to take the necessary enforcement actions.

The administrative capacity of the Authority should be complemented by an effective inspectorate suitably trained and mandated to monitor compliance with legislation.

This module is intended to ensure that all activities in drug manufacturing, import, export, distribution, etc. comply with the regulatory and quality assurance requirements, as well as with regulations. Inspection activities require motivated, well-trained and properly remunerated staff. WHO's guidelines on inspection are available, and contain the quality system framework for the NRA's inspectorate, check-lists for inspectors, sample forms, standard formats for reports and other useful references.

Adequate assessment of regulatory inspection and enforcement activities may require a review of how other relevant law enforcement offices attached to the related Governmental agencies or authorities are involved in these activities.

The assessor should find out how the NRA has established its enforcement strategies to promote compliance with drug regulations. These strategies should be based on a pyramid of sanctions that have to apply in a proportionate manner relative to the non-compliance identified. Proper internal procedures should be established and implemented.

The assessor should identify the unit of the NRA which is responsible for such enforcement activities to determine if any conflict of interests can be avoided and to demonstrate the independence in decision-making.

The NRA should maintain a close collaboration with the other enforcement agencies, the police and the courts of justice that might intervene in the pharmaceutical sector.

13.1. Legal basis

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

There should be legal provisions to inspect the premises/facilities of market authorization holders, manufacturers, research institutions, importer and exporter’s agents, distributors, wholesalers, retailers and other distribution channels (pharmacists, dispensing doctors etc.) based on the applicable standards.

There should be legal provisions to inspect the above-mentioned activities for all categories of pharmaceutical products.

There should be legal requirement for compliance with the current good practices (e.g. Good Manufacturing Practices, Good Clinical Practices, Good Laboratory Practices, Good Distribution Practices, Good Vigilance practices, Good dispensing practices, etc.)

The law should attribute to the inspectors adequate powers and authority to perform their duties, in particular:

- to inspect at any reasonable time any place where the regulated products are manufactured, packaged, stored, distributed, tested or sold
- to take samples
WHO Guidance for the assessment of drug regulatory systems

- to make copies of documents
- to take photographs of premises and equipment
- to seize or detain the regulated products believed to be in violation
- to open and examine any receptacle or package that contains articles subjected to the relevant legislation
- to receive full cooperation of staff of the inspected premises who must not obstruct the investigations being performed.

The assessor should be able to determine if the scope of the inspection and enforcement activities covers the whole scope of the requirements which have to be fulfilled by stakeholders.

13.2. Guidelines

The assessor should review the guidance published for all kinds of stakeholders and find out if the guidance covers the scope of the applicable legislation and regulation. If applicable, the assessors should check the coherence with the WHO's guidance to identify if the minimum requirements of WHO are met. Any differences should be identified and justified.

13.3. Organization and structure

The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations as well as how the exchange of information is established and implemented.

13.4. Quality management system

The assessor should review the quality management system implemented within the inspectorate and compliance with the requirements on quality management systems that should have been taken as reference. A WHO guidance document or an international standard on quality management system might be used as a reference. In any case, the questionnaire included in this module relates to the main quality management system issues.

13.5. Internal planning and procedures

The assessor should review the inspection and enforcement procedures regarding their expected outcomes, their level of detail relative to the training provided and the measures applied to check the performance of the described activities.

The assessor should pay particular attention to review their coherence with the applicable guidance, regulations and legislation.

The following indicators can help the assessor to determine the level of enforcement activities that are performed:

- Number of administrative measures issued (QI 13.16),
- Number of licenses withdrawn or suspended (QI 13.18),
- Number of criminal prosecutions submitted (QI 13.19),
- Number of legal sanctions applied (QI 13.20)
- Average number of days for taking an administrative measure (QI 13.17)
13.6. **Human and other resources**

The assessment of human resources should focus on two aspects: quantitative and qualitative. Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Number of inspectors involved per inspection category (QI 13.3, QI 13.7 and QI 13.11)
- Number of facilities inspected per inspection category (QI 13.4, QI 13.5, QI 13.8, QI 13.9 and QI 13.12) compared to the number of facilities licensed per inspection category (QI 5.2, QI 5.3, QI 6.2, QI 6.3 and QI 7.2)
- Average number of days spent on site per inspection category (QI 13.6, QI 13.10 and QI 13.13)

These indicators should enable the assessor to determine the coverage of the inspectorate activities and the level of scrutiny that is applied to the stakeholders and by consequence should give information on the level of compliance of these stakeholders to the applicable regulation.

The assessor should review the adequacy of the competencies of the inspectors, and should determine in particular if they have the following competencies for GMP inspection:

- academically qualified in a recognized scientific/technological discipline related to pharmaceuticals;
- personal experience in pharmaceutical manufacturing or drug control;
- satisfactorily completed a recognized training course on auditing of quality management systems;
- undergone at least 10 days of training per year (e.g. courses, symposia, conferences, etc.);
- competent working knowledge of the applicable guidelines on GMP for pharmaceutical products and/or the GMP inspection procedures of the NRA;
- undergone an appropriate training in the current procedures and techniques for GMP inspections before conducting an inspection alone;
- have the necessary personal qualities of integrity, tact and character to perform the duties of a GMP inspector.

The assessor should also find out if the inspectors have the necessary logistical support in order to perform their mission and to complete the planned activities.

13.7. **Records and outputs**

The assessor should review how all the information collected during the licensing process is managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedure of the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes such as Marketing authorization or licensing premises.

13.8. **Availability of information**

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.
Documented evidence to be studied

- Acts, Laws, Decrees
- Publications, guidance
- Quality policy and objectives
- Quality manager designation and job description
- Inspection quality manual
- Management review minutes
- Procedure for documentation control
- Inspection Plans
- List of equipment (logistics, computer, etc.)
- Procedure for planning, implementing internal audit and following up with corrections
- Audit reports and follow-ups
- Quality indicators (timeframe, reporting)
- Procedure for investigation of non-compliances and records
- Procedure for initiation, decision and implementation of corrective and preventive actions and to check efficiency and records
- Procedure for dealing with complaints and recalls
- Procedure for inspection (preparation, planning, realization and follow-up)
- Procedure for sampling and records
- Inspection report format
- Inspection reports
- Inspection planning for a specific year
- Procedure to issue or to withdraw of GXP certificate
- Procedure to issue or to close premises, warning letter/notice of non-compliance
- Procedure for recruiting, training and qualifying inspectors with periodic re-qualification and records
- List of inspectors with their scope of intervention
- List of facilities inspected
- List of warning letters/notices of non-compliance issued
- Certificate format/template

Reference:


14. Quality Control Laboratory - Module 14

Objective:
To assess the organization set in place for the testing of pharmaceutical products

Drug quality control laboratories are responsible for checking, by appropriate testing, whether drugs are of the required quality before and after commercialization. The resources and technical capacity to carry out these activities at country level vary enormously, but each NRA should have access to a quality control laboratory, which will also play an important role in the registration process and in the surveillance of the quality of marketed products.

It is generally recommended that all countries should have access at least to a small laboratory where basic tests can be performed and that such basic facilities are gradually expanded. The tests might be performed properly and more cost-effectively in an already existing institution, such as a University Pharmacy Department or an independent laboratory.

14.1. Legal basis
The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

14.2. Guidelines
The assessor should review the guidance published for all kinds of stakeholders, and find out if the guidance covers the scope of the applicable legislation and regulations. Coherence with WHO guidance should be checked and any differences should be identified.

14.3. Organization and structure
The assessor should identify the organization set in place to exert the regulatory functions; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organization and how the exchange of information is established and implemented.

14.4. Quality management system
The assessor should review how the organization satisfies the requirements on quality management systems that have been taken as reference. This reference might be a WHO guidance document or an international standard on quality management systems. In any case, this questionnaire addresses the main Quality management system issues.

14.5. Quality control procedures
The assessor should review the procedures with regards to their expected outcomes, their level of detail and adequacy in relation to the training provided and the measures applied to check the performance of the described activities.

The assessors should particularly review their coherence with the applicable guidance, regulations and legislation.

14.6. Human resources
The assessment of human resources should focus on two aspects: quantitative and qualitative.
Regarding the quantitative aspects the assessor can decide to use the following indicators to identify if adequate human resources are made available to exert the planned activities:

- Number of scientific staff involved in the testing activities (QI 14.8)
- Number of pharmaceutical products tested and certificates issued per product category (QI 14.1, QI 14.2, QI 14.3 and QI 14.4)
- Number of pharmaceutical products tested (QI 14.5) and failed to be compliant (QI 14.5.1)

The following indicators should enable the assessor to determine the participation of the quality control laboratory activities in the compliance activities:

- Number of pharmaceutical products tested per product category (QI 14.1 and QI 14.4) compared to the number of authorizations granted per category (QI 4.3 and QI 9.1)
- Number of pharmaceutical products recalled based on the results issued by DCL (QI 14.6),
- Number of MA suspended or withdrawn based on the results issued by DCL (QI 14.7)

The assessor should review the adequacy of the competencies of the personnel involved in the quality control processes in particular as regards the following qualifications: the analysts should be graduates in pharmacy, analytical chemistry, microbiology or other relevant subject and the appropriate training should be provided for specific disciplines or techniques (Spectrophotometry, Instrumentation, etc).

### 14.7. Infrastructure and equipment

The assessor should review the availability and the adequacy of the equipment for performing the tests.

The assessor should particularly assess the adequacy of the premises, the work environment and workspace. The following indicators can be used by the assessors:

- Number of scientific staff involved in the testing activities (QI 14.8)
- Surface of the QCL (QI 14.9)
- Number of scientific staff compared to the surface ((QI 14.8/QI 14.9)
- Number of analysis not performed because of lack of adequate equipment (QI 14.10)

### 14.8. Reference standards/materials and reagents

The assessor should evaluate the procedures in place for purchasing, preparation, handling and testing of reference standards/materials and reagents.

### 14.9. Safety programme

The assessor should check the availability of the safety program and any measures to verify its effectiveness.

### 14.10. Subcontracting

The assessor should review how the Drug Control laboratory manages the analyses that are subcontracted to another laboratory/institution.
14.11. Records and outputs

The assessor should review how all the information collected during analysis are managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedure of the organization, the assessor will sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes such as marketing authorization.

Documented evidence to be studied

- Acts, Laws, Decrees
- Laboratory Information File
- Quality policy and objectives
- Quality manager designation and job description
- Quality manual
- QCL Management review records
- Procedures for documentation control
- Testing Plan or program
- List of equipment
- Procedures for planning, implementing internal audit and following up with corrections
- Audit reports and follow-ups
- Quality indicators (timeframes, reporting)
- Procedures for investigations of non-compliance and records
- Procedures for dealing with complaints and records
- Procedures for initiation, decision and implementation of corrective and preventive actions and check efficiency and records
- Internal procedures for the management of sample
- Internal procedures for testing, analytical validation, equipment qualification, maintenance; calibration and records
- Equipment maintenance planning
- Retesting policy
- Internal procedures for handling out of specification results
- Internal procedures for handling reference materials and reagents
- Organigram
- Training plan and follow-ups on its implementation
- List of staff with their qualifications
- List of equipment
- List of maintenance and calibration activities
- List of proficiency studies in which NCL has participated
WHO Guidance for the assessment of drug regulatory systems

- Logs books
- Map of the laboratory
- Safety guidelines
- Contracts for activities subcontracted
- List of analyses subcontracted

Reference:

Basic Tests for Drugs - Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms (WHO; 1998; 100 pages)


Quality Control Methods for Medicinal Plant Materials (WHO; 1998; 128 pages)


15. Control of Narcotics, Psychotropic Substances and Precursors - Module 15

**Objective:**

To assess the organization set in place for the control of narcotics, psychotropic substances and precursor chemicals.

The assessor should review the applicable legal requirements and find out if adequate regulations have been enacted.

The legislation should provide for adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation. (see regulatory inspection for enforcement and compliance activities)

The assessor should review the guidance published for all kinds of stakeholders, and find out if the guidance covers the scope of the applicable legislation and regulations. Coherence with WHO guidance should be checked and any differences should be identified.

A NRA should have at its disposal a legal framework with a well defined scope for the control of narcotics, psychotropic substances and precursor chemicals (NPSP). If the country of the NRA is a signatory to the International Conventions on the Control of Narcotics, Psychotropic Substances and Precursors, the NRA is likely to have access to the needed information on the control of the above-mentioned substances.

For operational purposes the NRA should have the proper regulations for the control of NPSP. There should be specific requirements for their manufacturing, importing, exporting, storage, distribution, consumption, reporting, reconciliation and disposal. Guidelines on the formats for permits, forms for advice of receipt and submission of returns are necessary as well.

For effective communication between the NRA and the institutions and facilities involved, there is need for the designation of a focal person on the control of NPSP by the institution/facilities involved. The NRA should have the appropriate procedures to evaluate the returns for quantification and detection of abuses or diversions, as well as documented procedures for decision-making on recommended action to be taken by the NRA on defaulters. There is need for the NRA to have adequate personnel with requisite training in the control of NPSP.

The activities required for the control of NPSP vary from one country to the other. In some countries, the activity is centralized while in others it is decentralized or delegated to other agencies or institutions. If the latter applies, a coordinating body is necessary. The role of civil society and healthcare professionals in the activities for the control of NPSP should be encouraged.

For effective control of NPSP the reporting time lines should be well defined as well as the means of submitting returns, a database on consignments received, returns submitted and any abuse or diversions and actions taken should be available.

Furthermore information sources and reference materials on the control of NPSP should be readily available.

The assessor should review how all the information collected during the processes are managed, what kind of information is registered and archived by the organisation.

While reviewing the implementation of the internal procedures of the organization, the assessor should sample the records generated and check their contents. The assessor should check if output from this process will become an input for the linked processes.
The assessor should identify the organization set in place to exert the regulatory function; if the same function is delegated or decentralized and in particular what level of the country (central, regional or local level) is mobilized. If different organizations at different levels of the state are involved the assessor should review the linkages among the organizations as well as how the exchange of information is established and implemented.

The assessor should review which kind of information is publicly available, if the media used (web page, official gazette or other NRA bulletin) are appropriate and if the information are maintained and updated on a regular basis.

**Documented evidence to be studied**

- Acts, Laws, Decrees
- Guidance published
- List of staff with their qualification
- Internal procedures
- List of focal persons

**Reference:**


16. **International cooperation and harmonisation - Module 16**

**Objective:**

To assess the organization set in place to participate in the harmonization processes to enhance cooperation and collaboration among regional or international NRAs.

The aim of this module is to find out if the assessed organization cooperates with other similar organizations or works towards a harmonization or convergence process. Because of regulatory complexities and extent of scientific expertise required, International cooperation and regional or subregional collaboration are encouraged as a way to share experiences, best practices and competences. In some cases, mutual agreements, recognition or memoranda of understanding between countries can permit recognition/taking into consideration of decisions, authorizations or registrations of other regulatory authorities.

The assessor should also review the involvement of the DRA in its regional and international environment, if the ways of communication are set and if operational collaboration is established.

**Documented evidence to be studied**

- Conventions
- Mutual recognition agreements
- Memoranda of understanding signed
- Requests sent to/received from other DRAs for inspection, information on registered products or on pharmacovigilance issues

**Reference:**


*International Pharmacopeia*


WHO Monographs on Selected Medicinal Plants - Volume 1 (WHO; 1999; 295 pages)

WHO Monographs on Selected Medicinal Plants - Volume 2 (WHO; 2004; 358 pages)
**Glossary**

The terms listed below are defined specifically for the purposes of this manual. They may be defined differently in other documentation, including annexes in this manual which were, in certain cases, published some years ago.

**accountability**

Being required to account for one’s conduct and actions, usually to an individual or group but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and transparency (see below).

**active pharmaceutical ingredient (API)**

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

**advertising**

For the purposes of this manual, advertising is considered a part of promotion.

**applicant**

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization, or a variation to an existing marketing authorization.

**assessment (report)**

See Evaluation Report

**authorized person**

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some other GMP guides and legal texts, the term qualified person is used to describe analogous functions.

**bioequivalence**

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

**comparator**

In this manual, the term comparator is used to mean “the pharmaceutical product with which the new product is intended to be interchangeable in clinical practice”. In any particular market, the comparator should be the first in this list that is available.

- the product for which efficacy, safety and quality have been fully established (often the innovator);
- a market leader that has been authorized for marketing after a process of assessment;
- a market leader that is legally marketed but has not been assessed prior to marketing authorization.

See Annex 2, section 16 for guidance on how to deal with the situation where the comparator proves, on testing, to be of poor quality, e.g. it has poor bioavailability.

**container labelling**

All information that appears on any part of a container, including that on any outer packaging such as a carton.
**dosage form**

The form of the completed pharmaceutical product, e.g. tablet, capsule, injection, elixir, suppository.

**drug**

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

**drug master file**

A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

**drug product**

See pharmaceutical product.

**drug regulatory authority**

A national body that administers the full spectrum of drug regulatory activities, including at least or all of the following functions:

- marketing authorization of new products and variation of existing products;
- quality control laboratory testing;
- adverse drug reaction monitoring;
- provision of drug information and promotion of rational drug use;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.
- Control of clinical trials

**essential drugs**

Essential drugs are those that satisfy the health care needs of the majority of the population. As indicated by the Expert Committee on the Use of Essential Drugs [12], each country may generate its own list of essential drugs.

**evaluation report**

A critical summary and interpretation of the data, with conclusions, prepared by or on behalf of the drug regulatory authority.

**excipient**

Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

**expert advisory body**

A standing advisory board (or committee) of independent experts, including academic experts and practicing health care professionals.

**expert report**

In European Union usage critical summary and interpretation of the data, with conclusions, prepared by or on behalf of an applicant.

**finished product**

A product that has undergone all stages of production, including packaging in its final container and labelling.
**formulation**

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

**generic products**

The term *generic product* has somewhat different meanings in different jurisdictions. Use of this term is therefore avoided as much as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the innovator products. Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

**innovator pharmaceutical product**

The innovator pharmaceutical product is generally that which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorization). When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

**interchangeability**

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

**labelling**

The word “labelling” has been avoided in this manual because its meaning is not consistent between Member States. See *container labelling* and *product information*.

**licence**

See *marketing authorization*.

**manufacture (manufacturing)**

All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

**marketing authorization**

An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform with all the details provided in your application and as modified in subsequent correspondence”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.
Once a product has been given marketing authorization, it is included on a list of authorized products - the register - and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a licence or product licence.

Marketing authorization holder

The person or company in whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorization holder must be subject to legislation in the country that issued the marketing authorization, which normally means being physically located in the country.

master file

A master file is a dataset that is:

- submitted by someone other than a finished product applicant, e.g. the supplier of an active ingredient or the supplier of a packaging component;
- a common feature of more than one product, e.g. sterility test procedures; or
- some other matter that is conveniently dealt with by means of a master file.

An applicant for a new marketing authorization or for a variation may make reference to a master file, but must have the permission of the person or company that submitted the master file.

medicine

See drug.

medicinal product

See pharmaceutical product.

multisource (generic) pharmaceutical product

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

new chemical or biological APIs (new APIs)

New chemical or biological APIs are those not previously authorized for marketing for any pharmaceutical use in the country in question. Those provisionally authorized at the time of the initial market inventory are not new pharmaceutical ingredients.

new drug

Any drug that does not match the definition of well established drugs (see below).

new pharmaceutical product

A pharmaceutical product that contains a new API, a new combination of marketed APIs, or a new multisource (generic) product. It may be available either on prescription or without prescription.

newer drug

See new drug.

periodic review

The regular process, usually occurring every five years, by which the validity of a marketing authorization is renewed and information on a product is reviewed (validated), consolidated and sometimes expanded.
pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

product information

A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorization holder. The minimum information in the product information should be defined by the DRA. The content of the product information is agreed between the marketing authorization holder and the DRA at the time the market authorization is issued.

promotion

All informational and persuasive activities by marketing authorization holder, manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal products.

provisional marketing authorization

Temporary authorization following the initial market inventory, and pending full approval based on evaluation of quality, safety and efficacy.

provisional registration

See provisional marketing authorization.

quality control

Quality control is concerned with sampling, specifications and testing, and with the organization, documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

register

A list of all the pharmaceutical products authorized for marketing in a particular country. The register is maintained by the drug regulatory authority of the country in question.

registered drug products

Pharmaceutical products that have a marketing authorization.

registration

See marketing authorization.

renewal

The word “renewal” has been avoided in this manual because it’s meaning is not consistent between Member States. See periodic review and retention fee.
retention fee (for marketing authorization)
A fee paid to maintain marketing authorization, usually annually. Product details are not normally reviewed when retention fees are paid. (See also periodic review)

specification - expiry, check or shelf life
The combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf-life.

specification - release
The combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

stability
The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological and biopharmaceutical aspects of stability must be considered:

starting material
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

therapeutic equivalence
Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro studies.

tracking
Keeping a record of the progress of an application at all stages.

transparency
The term transparency means (1) defining policies and procedures in writing and publishing the written documentation, and (2) giving reasons for decisions to the affected party. There is some overlap between transparency and accountability (see above).

unregistered drug products
Pharmaceutical products that do not have a marketing authorization.

update
See periodic review.

Validation
The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Variation
A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling, and product information.
well-established drugs

APIs (not products) which:

- have been marketed for at least five years in countries that undertake active postmarketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

See also well established drug combinations and well established drug products.

Because this definition refers to active pharmaceutical ingredients and not products, it does not take into account possible sensitivities to excipients and other factors that are relevant to therapeutic equivalence.

well-established drug combinations

Combinations of drugs which:

- have been marketed for at least five years in countries which undertake active postmarketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

See also well established drugs and well established drug products.

Because this definition refers to active pharmaceutical ingredients and not products, it does not take into account possible sensitivities to excipients and other factors that are relevant to therapeutic equivalence.

well-established drug products

Pharmaceutical products which contain well established drugs, and which:

- have been marketed for at least five years in countries that undertake active post-marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

WHO-type certificate

A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce
 Abbreviations

API  Active pharmaceutical ingredient
ADR  Adverse drug reaction
BP   British Pharmacopoeia
CT   Clinical trial
NRA  National regulatory authority
EMEA European Agency for the evaluation of medicinal products
EP   European Pharmacopoeia
GCP  Good clinical practices
GDP  Good distribution practices
GLP  Good laboratory practices
GMP  Good manufacturing practices
GXP  Good practices
ICH  International Conference for Harmonisation
IEC  Independent ethics committee
IRB  Institutional review board
MAH  Market authorisation holder
MoH  Ministry of Health
NDCL National drug control laboratory
NGO  Non-governmental organisation
NPSP Narcotics, psychotropic substances and precursor chemicals
OTC  Over the counter
PI   Product information
PhInt International pharmacopoeia
QMS  Quality management system
SPC  Summary of product characteristics
WHO  World Health Organisation
Annexes

These annexes include certain text already published by WHO and some new model documents. Materials published by WHO is updated from time to time; the most recent version will normally be the most relevant.
Annex 1: Terms of reference for the assessment Team

Background

Date and place

Purpose of the mission
- Review, in cooperation with the officials of the (name of NRA) of (Name of the country) the medicine regulatory situation and prepare a report on the assessment’s findings;
- Discuss the report with the relevant stakeholders to achieve consensus on its contents
- Develop a national action plan in cooperation with the officials of the (name of NRA) of (Name of the country)

Method of work:
- Interview officials of the (name of NRA) of (Name of the country) and other relevant technical staff
- Review the relevant documents, reports, etc
- Meet and discuss with other relevant people and stakeholders

Activities
- Visit the (name of NRA) of (Name of the country) and other relevant institutions
- Interview relevant officials and technical staff using the WHO data collect tool and other relevant documents
- Interview, if necessary, relevant pharmaceutical business associations, professional associations such as pharmacy and health associations etc
- Review the documents, country’s reports/studies already existing
- Write a draft assessment report indicating the main gaps ascertained in medicines regulation, as well as possible recommendations for improvement.
- Discuss the draft assessment report with the relevant stakeholders and finalize the report
- Develop a national action plan in cooperation with the officials of (name of NRA) for improving medicine regulation in (Name of the country)

Expected outcomes
- Medicine’s regulation assessment report
- Completed WHO data collection tool
- Plan of Corrective Action
Annex 2: Recommended Regulatory Assessor’s Competencies.

**Education**
Essential: University Degree/Qulification in pharmaceutical science or another equivalent degree/qualification
Desirable: advanced training in medicine regulation

**Experience**
Essential: At least 5 to 7 years of experiences in medicine regulation (Drug registration, Licensing/Regulatory Inspection or Laboratory control) at national level required in applying and interpreting the drug-related regulations and guidance
Desirable: International experience in medicines’ regulation particularly in developing countries.

**Languages**
Essential: Working knowledge of English or French
Desirable: Basic knowledge of the official language of the country assessed would be an asset.

**Competencies**
An assessor must;

- Demonstrate formulation and synthesis skills
- Demonstrate adequate knowledge and use of computer applications needed in the Regulatory Assessment environment
- Demonstrate investigative and analytical skills
- Foster the cooperation, communication, and consensus within and among groups and meetings to accomplish a common goal
- Demonstrate the ability to structure and organize work as well as to set priorities and to meet deadlines
- Demonstrate technical skills in the production of written materials related to the medicine regulation
Annex 3: Example of a Confidentiality Agreement

CONFIDENTIALITY UNDERTAKING BY TEAM MEMBERS PARTICIPATING IN THE REVIEWS OF NATIONAL REGULATORY SYSTEM

While visiting and assessing Member States as an expert adviser the assessor will have access to certain information belonging to the assessed institutions. Such information (hereafter referred to as “the Information” should be considered and handled as confidential and proprietary to the aforesaid parties.

In this connection, I agree:

1. not to use the Information for any other purposes other than those requested by this mission; and

2. not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained in this document.

However, I will not be bound by any obligation of confidentiality and non-use to the extent that I am clearly able to demonstrate that any part of the Information:

1. was known to me prior to any disclosure by or on behalf of the institutions assessed; or

2. was in the public domain at the time of disclosure by or on behalf of the institutions assessed; or

3. could become part of the public domain through no fault of my own.

Furthermore I undertake not to communicate my findings and/or those of the team of experts in which I will participate, as well as any resulting recommendations and/or decisions to any third party, except if explicitly requested in writing.

I confirm that the information disclosed by me in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interests is known to me.

I undertake to promptly advise of any change in the above circumstances, including if an issue arises during the course of my work.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _______________________________
Name (typewritten) _______________________________
Institution _______________________________
Place ________________ Date ________________
Annex 4: Example of a Declaration of no conflicting Interest by Assessors

DECLARATION OF NO CONFLICTING INTERESTS
BY TEAM MEMBERS PARTICIPATING IN REVIEWS OF A NATIONAL REGULATORY SYSTEM

While visiting and assessing Member States as an expert adviser the assessor will have access to certain information belonging to the assessed institutions. Such information (hereafter referred to as “the Information” should be considered and handled as confidential and proprietary to the aforesaid parties.

In this connection, I declare that:

- I will discharge my functions exclusively as an adviser;
- no situation of real, potential or apparent conflict of interest is known to me, including that you I no financial or other interest in, and/or other relationship with, a party, which:
  - may have a vested commercial interest in obtaining the access to any confidential information obtained in the course of the review visit, and/or
  - may have a vested interest in the outcome of the review visit including, but not limited to, parties such as manufacturers of medicines or vaccines.

I undertake to promptly advise of any change in the above circumstances, including if an issue arises during the course of my work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _________________________________________
Name (typewritten) _______________________________
Institution ________________________________________
Place ________________ Date _____________________
### Annex 5: Draft program of a Regulatory Assessment

**DRAFT PROGRAM FOR THE ASSESSMENT OF A DRUG REGULATORY SYSTEM**

**DATE**

Provisional program

<table>
<thead>
<tr>
<th>Time</th>
<th>Activities</th>
<th>Person involved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monday</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94x570</td>
<td>Arrival</td>
<td></td>
</tr>
<tr>
<td>94x551</td>
<td>Meeting with representatives of donors</td>
<td></td>
</tr>
<tr>
<td>94x531</td>
<td>Meeting with representatives of MoH</td>
<td></td>
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<tr>
<td>94x511</td>
<td>Meeting with the Head of the regulatory authority</td>
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<tr>
<td>94x491</td>
<td>Review of background documents</td>
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<tr>
<td><strong>Tuesday</strong></td>
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<tr>
<td>08 00 – 09 00</td>
<td>Planning and Preparation of the assessment program</td>
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<tr>
<td>09 00 – 10 00</td>
<td>Meeting with the Heads of departments</td>
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<tr>
<td>10 00 - 11 00</td>
<td>Visit of the Human Resource and Administration Department</td>
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<tr>
<td>11 00 – 12 00</td>
<td>Visit of the Finance department</td>
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<tr>
<td>12 00 - 13 00</td>
<td>Lunch</td>
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<tr>
<td><strong>Drug Evaluation and Registration</strong></td>
<td>Visit of the Medicines evaluation and registration unit</td>
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<tr>
<td><strong>Inspectorate</strong></td>
<td>Visit of the Premises inspection unit</td>
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<tr>
<td>13 00 - 15 00</td>
<td>Visit of the Herbal/Traditional Medicines evaluation and registration unit</td>
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<tr>
<td>15 00 - 17 00</td>
<td>Visit of the Narcotics and Psychotropics unit</td>
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<tr>
<td>15 00 - 17 00</td>
<td>Visit of the Port of Entry Activities unit</td>
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<tr>
<td><strong>Wednesday</strong></td>
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<tr>
<td>09 00 – 10 00</td>
<td>Visit of the Licensing department</td>
<td></td>
</tr>
<tr>
<td>10 00 – 10 30</td>
<td>Move to the NDQCL</td>
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<tr>
<td>10 30 - 12 00</td>
<td>Meeting with NDQCL staff</td>
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<tr>
<td>12 00 - 13 00</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13 00 - 14 00</td>
<td>Visit of the National Medical Stores/procurement agencies</td>
<td></td>
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<tr>
<td>Time</td>
<td>Activity</td>
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<tr>
<td>14 00 – 15 00</td>
<td>Meeting with representatives of the School of Pharmacy</td>
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<tr>
<td>15 00 - 16 00</td>
<td>Meeting with representatives of the Pharmaceutical Society</td>
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<tr>
<td>16 00 - 17 00</td>
<td>Meeting with representatives of the Hospital Association</td>
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<tr>
<td><strong>Thursday</strong></td>
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<tr>
<td>09 00 - 10 00</td>
<td>Meeting with the Pharmaceutical Services Department, MoH</td>
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<tr>
<td>10 00 - 11 00</td>
<td>Meeting with the members of the Pharmacy Board</td>
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<tr>
<td>12.00 - 13 00</td>
<td>Lunch</td>
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<tr>
<td>13 00 - 15 00</td>
<td>Visit to a Pharmaceutical's manufacturer</td>
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<tr>
<td>15 00 - 16 00</td>
<td>Visit to a wholesaler/Importer (Human and Veterinary)</td>
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<tr>
<td>16 00 - 17 00</td>
<td>Visit to a Retail Pharmacy and Medicine Store</td>
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<tr>
<td><strong>Friday</strong></td>
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<tr>
<td>08 00 – 11 00</td>
<td>Report writing and development of action Plan</td>
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<td>11 00 - 12 00</td>
<td>Debriefing with the Regulatory Authority staff</td>
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<tr>
<td>12 00 – 13 00</td>
<td>Lunch</td>
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<tr>
<td>13 00 - 15 00</td>
<td>Discussion on the report with Regulatory authority management</td>
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<tr>
<td>15 00 - 17 00</td>
<td>Planning for the corrective actions</td>
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<tr>
<td><strong>Saturday</strong></td>
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<tr>
<td>08 00 – 11 00</td>
<td>Planning continuation and finalization of the report.</td>
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<tr>
<td>11 00 - 12 00</td>
<td>Debriefing with representatives of MoH</td>
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</table>
Annex 6: List of institutions to be visited and Personnel to be met

During the assessment visit the meetings with the following parties should be planned:

- Ministry of Health / Ministry of industry,
- Representatives of the Regulatory authority and any other organizations involved in the regulatory functions,
- Staff of Regulatory authority or organization,
- Representatives of the Industry Association of manufacturers, distributors, importers and exporters,
- Representatives of the Professional Association of general practitioners, nurses and pharmacists
- Professionals Councils (Medical Practitioners Council, Pharmacists Council)
- Representatives of Consumer associations,
- Journalists.
- Non-governmental associations/organisations
- Procurement agencies, National medicines stores
- Health research organizations
- Chairmen or representatives of Advisory committee
- Chairmen or representative of IRB / IEC
- Representative of university academia
- Others
Annex 7: Example of the contents of an assessment Report
Format

Medicine Regulatory Authority Assessment Report

Table of Contents

Abbreviations

Executive Summary and main recommendations
1. General information on the assessment
   1.1. Purpose of the assessment
   1.2. Place and date of the assessment
   1.3. Method of work
   1.4. Members of the mission
2. General information on the country
3. Findings and recommendations
   3.1. Organization of the national regulatory system
   3.2. Legislation and regulations
   3.3. Regulatory authority
      3.3.1. Human resources
      5.3.3 Regulatory tools
      5.3.4 Infrastructure
      5.3.5 Transparency and accountability
      5.3.6 Information Technology (IT)
   3.4. Regulatory functions
      3.4.1 Product Registration
      3.4.2 Regulatory Inspections and enforcement
      3.4.3 Licensing of manufacturers, importers, exporters, wholesalers and retailers
      3.4.4 Registration of pharmacy professionals
      3.4.5 Clinical trials
      3.4.6 Import and export controls
      3.4.7 Market controls
      3.4.8 Control of advertising and promotion of medicines
      3.4.9 Pharmacovigilance
      3.4.10 Quality Control
4. Conclusions and recommendations

Acknowledgments

Annexes

Annex 1 Completed data collection tool
Annex 2 List of organizations visited
Annex 3 List of persons met
Annex 4 List of documents provided
Annex 5 NRA’s organogram
Annex 6 List of persons that participated in the discussion on the report
Annex 7 List of people that participated in the preparation of the action plan
Annex 8 Action plan
Annex 8: Example of a format for a Plan of corrective actions

Date:
Country:
Name of Drug Regulatory Authority:
Prepared by: (name of assessors, name of NRA staff)

Period covered:

<table>
<thead>
<tr>
<th>Reference Findings to.</th>
<th>Recommendations</th>
<th>Objective to be achieved</th>
<th>Main tasks / activities to be performed</th>
<th>Timeframe</th>
<th>Responsible person</th>
<th>Resources required</th>
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</table>
Annex 9. Example of a format of a implementation report

Date:
Country:
Name of Drug Regulatory Authority:
Prepared by : (name of assessors, name of NRA staff)

Period covered:

<table>
<thead>
<tr>
<th>Objective to be achieved</th>
<th>Main tasks / activities to be performed</th>
<th>Timeframe</th>
<th>Activities implemented</th>
<th>Activities on-going, gaps with Level of implementation</th>
<th>Comments or proposition</th>
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</table>
Annex 10. Quantitative indicators for regulatory purposes

Module 3 - Regulatory Authority
QI 3.1 - Total number of the NRA's employees at the end of a reference year
QI 3.2 - Number of the NRA's scientific staff performing regulatory functions
QI 3.3 - Number of the NRA's support staff
QI 3.4 - Number of the NRA's staff IT specialist
QI 3.5 - Number of the NRA's staff involved in QMS
QI 3.6 - Number of the NRA's staff recruited in the reference year
QI 3.7 - Number of the NRA's staff's cancellation in the reference year

Module 4 - Marketing authorization
QI 4.1 - Number of scientific staff involved in the registration process
QI 4.2 - Number of products with a valid Marketing Authorization
QI 4.3 - Total number of applications received in the reference year
QI 4.4 - Number of applications received for a new drug in the reference year
QI 4.5 - Number of applications received for a generic product in the reference year
QI 4.6 - Number of applications received for variations in the reference year
QI 4.7 - Number of applications received for renewal in the reference year
QI 4.8 - Number of decisions taken (positive, refusals, suspension) in the reference year
QI 4.9 - Number of applications pending as backlog
QI 4.10 - Average number of days for decision-making on a new drug
QI 4.11 - Average number of days for decision-making on a generic product
QI 4.12 - Average number of days for decision-making on variations
QI 4.13 - Average number of days for decision-making on renewals

Module 5 - Licensing of manufacturers
QI 5.1 - Number of scientific staff involved in establishment licensing
QI 5.2 - Number of manufacturing plants licensed
QI 5.3 - Number of manufacturing plants of API licensed
QI 5.4 - Number of applications received for a new premise in the reference year
QI 5.5 - Number of modifications of an initial license received in the reference year
QI 5.6 - Number of decisions taken (positive negative, suspension or withdrawn) in the reference year
QI 5.7 - Number of applications pending as backlog
QI 5.8 - Average number of days to issue a decision

Module 6 - Licensing of importers, exporters, wholesalers and distributors
QI 6.1 - Number of scientific staff involved in establishment licensing
QI 6.2 - Number of licensed wholesalers, importers and exporters
QI 6.3 - Number of licensed wholesalers, importers and exporters of API
WHO Guidance for the assessment of drug regulatory systems

QI 6.4 - Number of applications received for a new premise in the reference year
QI 6.5 - Number of modifications of an initial license received in the reference year
QI 6.6 - Number of decisions taken (positive, negative, suspension or withdrawn) in the reference year
QI 6.7 - Number of applications pending as backlog
QI 6.8 - Average number of days to issue a decision

Module 7 - Licensing of pharmacies and retail outlets
QI 7.1 - Number of scientific staff involved in establishment licensing
QI 7.2 - Number of licensed pharmacies and dispensing/selling outlets
QI 7.3 - Number of applications received for a new premise in the reference year
QI 7.4 - Number of modifications of an initial license received in the reference year
QI 7.5 - Number of decisions taken (positive, negative, suspension or closed) in the reference year
QI 7.6 - Number of applications pending as backlog
QI 7.7 - Average number of days to issue a decision

Module 8 - Registration of pharmacy personnel
QI 8.1 - Number of administrative staff involved in registration of pharmacy personnel
QI 8.2 - Number of pharmacist and pharmaceutical technicians registered
QI 8.3 - Number of application received in the reference year
QI 8.4 - Number of decisions taken (positive, negative, suspension or radiation) in the reference year
QI 8.5 - Average number of days to issue a decision

Module 9 - Market surveillance

Import and export Control
QI 9.1 - Number of application received (import and export)
QI 9.2 - Number of authorizations for importation granted in the reference year and/or number of product authorized for importation
QI 9.3 - Number of certificates for export issued in the reference year
QI 9.4 - Average number of days to issue these administrative document

Market Control
QI 9.5 - Number of products monitored
QI 9.6 - Number of products detected as non-compliant or of poor quality in the reference year

Non-compliant Products / Recall Procedures
QI 9.7 - Number of complaints on pharmaceutical products received in the reference year
QI 9.8 - Number of products/batches recalled in the reference year

Module 10 - Control of drug promotion
QI 10.1 - Number of staff involved in the control of drug promotion
QI 10.2 - Number of drugs advertisement applications received in the reference year
**WHO Guidance for the assessment of drug regulatory systems**

**Module 10 - Drug Promotion and Advertising**

QI 10.3 - Number of promotion and advertisement document monitored

QI 10.4 - Number of decisions taken (approbations, refusals, suspensions) on drug advertisement in the reference year

QI 10.5 - Average number of days for decision-making on drug promotion

QI 10.6 - Number of drug advertisements found to be in violation of the regulation and withdrawn in the reference year

**Module 11 - Pharmacovigilance**

QI 11.1 - Number of NRA's professionals involved in the assessment and management of ADR/ADE

QI 11.2 - Number of contact points (moral or physical person having sent an ADR/ADE)

QI 11.3 - Number of ADR/ADE reported by MAH. Manufacturers, importers or distributors and assessed in the reference year

QI 11.4 - Number of ADR/ADE reported by health professional/contact point and assessed in the reference year

QI 11.5 - Number of ADR/ADE reported by patients and assessed in the reference year

QI 11.6 - Number of periodic report received and assessed in the reference year

QI 11.7 - Number of decisions taken (no action taken, product recall, Dear doctor letters, notices for users, etc…) in the reference year

QI 11.8 - Number of ADR/ADE reported pending as backlog

QI 11.9 - Average number of days for decision-making on pharmacovigilance issues

**Module 12 - Clinical trial**

QI 12.1 - Number of staff involved in the control of Clinical trial

QI 12.2 - Number of clinical trials applications received in the reference year

QI 12.3 - Number of applications for amendments of clinical trials received in the reference year

QI 12.4 - Number of decisions taken (approvals, refusals, suspensions) on clinical trials applications in the reference year

QI 12.5 - Average number of days for decision-making for NRA

QI 12.6 - Average number of days for decision-making for IRB/IEC

QI 12.7 - Number of staff involved in the inspection of clinical trials

QI 12.8 - Number of clinical trials inspected in the reference year

QI 12.9 - Average number of days spent on-site per inspection

**Module 13 - Regulatory Inspection and enforcement activities**

QI 13.1 - Total number of inspectors for the pharmaceutical products sector

QI 13.2 - Total numbers of inspections carried out in the reference year

QI 13.3 - Number of manufacturing inspectors

QI 13.4 - Number of manufacturing facilities inspected including foreign manufacturers in the reference year

QI 13.4.1 - Number of manufacturing facilities inspected for pre-approval inspection for marketing authorization
QI 13.5 - Number of manufacturing facilities of API inspected in the reference year
QI 13.5.1 - Number of manufacturing facilities of API inspected for pre-approval inspection for marketing authorization
QI 13.6 - Average number of days spent on-site per manufacturing inspection
QI 13.7 - Number of importers, exporters, wholesalers and distributors inspectors
QI 13.8 - Number of wholesale/import/export facilities inspected in the reference year
QI 13.9 - Number of wholesale/import/export facilities of API inspected in the reference year
QI 13.10 - Average number of days spent on-site per wholesale/import/export inspection
QI 13.11 - Number of inspectors for retail facilities
QI 13.12 - Number of retail facilities inspected in the reference year
QI 13.13 - Average number of days spent on-site per retail facility inspection
QI 13.14 - Number of facilities inspected on pharmacovigilance in the reference year
QI 13.15 - Average number of days spent on-site per facilities inspected on pharmacovigilance
QI 13.14 - Number of administrative measures (notice of non compliance or warning letters) issued in each of the last three years
QI 13.15 - Average number of days for taking an administrative measures such as a notice of compliance or a warning letter
QI 13.16 - Number of license withdrawn or suspended in each of the last three years for non-compliance issues
QI 13.17 - Number of criminal prosecution submitted to court and/or penal sanctions requested in each of the last three years
QI 13.18 - Number of legal sanctions applied by the judiciary in each of the last three years

Module 14 - Quality Control
QI 14.1 - Number of pharmaceutical products tested in the framework of an application for a MA in the reference year
QI 14.2 - Number of active pharmaceutical ingredients tested in the framework of an application for a MA in the reference year
QI 14.3 - Number of pharmaceutical products tested for import control in the reference year
QI 14.4 - Number of pharmaceutical products tested for market control in the reference year
QI 14.5 - Number of pharmaceutical products tested/certificate issued in the reference year
QI 14.5.1 - Number of pharmaceutical products tested and failed to be compliant
QI 14.6 - Number of pharmaceutical products recalled based on the results issued by DCL in the reference year
QI 14.7 - Number of MA suspended or withdrawn based on the results issued by DCL in the reference year
QI 14.8 - Number of scientific staff in the Quality Control laboratory
QI 14.9 - Surface of the Quality Control laboratory
QI 14.10 - Number of analysis not performed because of lack of adequate equipment
Annex 11. Main source of documented evidence

Regulatory system
- List of Act, Law, Decree or circular establishing the regulatory system

Regulatory authority
- Act, Law, Decree or circular establishing the Regulatory authority
- Corporate, strategic and business plan of the NRA
- Mission, vision, objectives and indicators of the NRA,
- Quality manual,
- List of Internal procedures
- List of internal forms and templates
- List of the fees applicable for licensing, registration or authorization
- Organigram/organization charts
- Code of conduct/code of ethics
- List of staff with their qualifications
- List of external experts
- Annual report, self-assessment report

Regulatory functions (Registration, Licensing manufacturers wholesalers and pharmacies, Inspection, Control of Clinical Trail, Pharmacovigilance, Market control, Import Control, Quality Control Laboratory, control of drug promotion)
- Act, Law, Decree or circular establishing legal provisions for each regulatory functions
- Guidance published on this domain
- Internal procedure
- List of equipment.

NOTE:
A request for documentation should be sent in advance to the organization assessed in order to prepare the assessment. The request should be consistent with the purpose and the scope of the assessment.
Annex 12. Overview of the assessment tool

History and background on the assessment tool

The guide for regulatory assessment contained in this document has been prepared by revising and refining the guide for data collection to assess drug regulation performance initially developed for by WHO’s Department of Medicines Essential drugs and medicines policy (EDM) in 2001. The initial guide was drafted by Mr Eshetu Wondemagegnehu based on the experience gained from field application. This guide has been further reviewed and refined by Department of Technical Cooperation for essential drugs and traditional Medicine (TCM) for distribution in the present form.

General information on the design

- Organization of the document

After the collection of general information on the country and on the global regulatory system the assessor should follow the structure of the WHO Data Collection Tool which is based on the main regulatory functions of a drug regulatory system: the registration of the pharmaceutical products, the licensing of the different actors, the regulatory inspection, the drug control laboratory, the monitoring of clinical trials, the control of drug promotion and advertisement, the monitoring of adverse events, post marketing surveillance, etc…

Based on these major regulatory authority functions the questioning methodology is always organized in the same way based on legislation, resources and outcomes

- Legislation, regulation and guidance

The questions at the beginning of each module relate to legislative and regulatory aspects. The legislative body of a country should provide the regulatory authority with the appropriate legislation to establish the general framework of the principles within which the government is expected to act and within which the regulations are issued. The regulations might be issued by the Government, by an individual minister, or by a designated authority within or under the supervision of a Ministry. The process of preparing or reviewing the legislation is usually time-consuming and complex, whilst the preparation and updating of regulations is a more dynamic process.

Therefore, the legislation does not need --and in fact it should not-- include detailed indications and prescriptions, but should only state general principles that do not require regular updating. Details on the application of such general principles should be included in regulations. For example: the legislation can establish the requirement for registration fees and indicate which operational body, e.g., the minister of health, should determine the amount and extent of the fees. Thereafter, the regulations issued by, in this example, the minister of health, should indicate and keep up to date the fee system.

The described legal aspects should be completed by documents elaborated by the authority in charge of the implementation and should describe, be explicit or give precise instructions on the legislative and regulatory requirements.: These documents should provide for a better understanding and implementation by the stakeholders such as manufacturers, importers or distributors. These documents might be referred to in different ways: guidance, guideline, instructions and can take different formats. However they should always be published, publicly available and disseminated in a proactive manner by the Regulatory authority.

- Internal Processes and adequate Resources

Afterwards the WHO Data Collection Tool deals with the internal aspects of the organization and particular attention is given to the administrative procedures established in the organization to perform its activities in a robust way. Internal and administrative procedures should describe the functioning of the regulatory authorities, responsibilities and define the decision-making processes.
Personnel should have the required educational qualifications and the competencies to assume their tasks. Adequate facilities, equipment and IT technologies should be provided.

Further questions deal with resource aspects that are needed by the organization to accomplish its assigned tasks: The kind and extend of resources can vary broadly as based on the kind of functions that have to be performed. For example the need for regulatory inspection relates more to manpower, competencies and training whereas in a drug control laboratory the issue will be adequacy of equipment.

The recognition and the use of the concept of risk management in the drugs area is fundamental for the establishment of effective preventive strategies. Drug regulatory authorities need to match control requirements to the available resources. In high-income countries, resources for drug control activities are considerable, hence eventual risks can be effectively kept at a very low level. In other countries, with limited resources at the disposal of regulatory authorities, the risk management approach applied to products, activities or practices should be considered in the definition of priorities, strategy and control measures.

• Technical Committees

For performing certain functions the regulatory authority should be encouraged to create ad-hoc technical or scientific committees of external experts for specific purposes (advisory, decision, etc.). For matters of transparency, the minutes of discussions, as well as the lists of participants to such committees should be publicly available. Some internal policies should deal with prevention of conflicts of interest.

• Outcomes of the regulatory processes

Finally the questionnaire reviews for each regulatory function the outcomes of the processes set in place by the organization and the availability of this information.

• Quantitative indicators

This methodology is completed by providing information to the assessor on quantitative indicators that can be useful during the performance of the assessment. The list of all the indicators mentioned in this guidance is provided as an annex (see annex 10). The assessment team can decide to request for this information before or during the assessment.

Various scopes of the tool

The methodology used to design this tool and the proposed organisation enable the assessor to apply it not only for pharmaceutical products but also for other health care products such as medical devices, cosmetics, etc. It will be up to the assessor when he defines the scope of the assessment to decide which category of products will be assessed. By consequence all the chapters that are applicable to pharmaceuticals can be repeated for the assessment of the other categories of products.

Various approaches for particular issues

This questionnaire can provide with a horizontal approach as well, for example as a matter of transparency or independence/impartiality or Information Technology management. For these cases specific checklists can be extracted from the questions of the tool.