



Pharmaceuticals: Drug Regulation in Low and Middle Income Countries

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Introduction

Most diseases in developing countries could be treated with existing and well-known medicines. However, essential pharmaceuticals often are not available, not accessible, or not used appropriately. As bad or worse, use of substandard and counterfeit drugs wastes money, and may cause treatment failures and unnecessary deaths.

A first step in providing access to quality medicines for all is to establish a sound regulatory system that guarantees that only safe and effective drugs are produced, imported and marketed, and provides guidance for appropriate use of these drugs.

Legislative framework

The WHO notes that drug regulation is an essential part of any country's national pharmaceuticals policy.[1] Drug regulation needs to flow from a legislative framework that provides the legal basis for a specialized government agency (such as the FDA in the United States) to interpret, implement and enforce laws regarding drug safety, efficacy and quality. It also needs to fit in with other policies that relate to health and industry.[2] In broad terms, legislation and regulations ensure that the responsibilities, qualifications, rights and roles of each party involved in the pharmaceutical business are defined and recognized. The law also defines how regulations are enforced and deviations penalized, in order to control the activities of drug manufacturing, import, export, marketing, prescribing, distribution and dispensing.

Key functions

The core elements of drug regulation cover the following activities:[1]

- Giving marketing authorization for medicines based on an assessment of quality, efficacy and safety.
- Approving the labeling for pharmaceutical products, based on international standards of readability, clarity, etc.
- If a national drug industry exists: certification of manufacturing sites based on Good Manufacturing Practice (GMP) standards.[3]

- Control and certification of all components of the pharmaceutical supply chain.
- Post-marketing surveillance activities, including monitoring of drug side effects and random sampling of registered medicines for quality control.
- Maintaining a medicines register, updated on a regular basis to include new information for example on side effects, new indications.
- Providing accurate drug information to the medical community and public, and controlling promotion and advertising activities.
- Approving clinical trial applications submitted by pharmaceutical manufacturers or academic institutions.

In some countries, the regulatory agency also has a price setting and price control function. This aspect is not discussed in this note, but will be covered in a separate Pharmaceuticals Brief.

Evaluation and marketing authorization for pharmaceuticals

Basically, countries have two options for organizing this task: they can assess quality, efficacy and safety of a new drug themselves, based on the scientific dossier provided by the manufacturer. In case of a new compound, a dossier can be a full truck load of documents. Alternatively, countries can base their decision on an assessment made by a foreign drug regulatory authority, for example the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).[4] The lack of standardization and transparency of regulatory processes makes mutual recognition between developing country authorities an exception. WHO has developed a certification scheme to facilitate trade in pharmaceuticals across borders, but many countries do not yet have the regulatory capacity required to fully implement this scheme.

High income, industrialized countries usually maintain a fully fledged registration authority that can evaluate a complete file from scratch. In some cases there is limited acceptance of registration decisions from other countries or some degree of collaboration between countries. In the EU, there is a central body that can issue licenses for the entire Single European Market, as well as national authorities that can issue a license for a specific country.

Middle income countries with limited financial or technical resources can implement a model based on acceptance of foreign marketing licenses, if saving costs for administration is a key issue. However, if there is a national pharmaceutical industry or if the country wants to provide market access for low cost generics imported from other developing countries, it must have at least the capacity to assess a generic drug dossier. This involves assessment of drug quality, compliance with Good Manufacturing Practice (including inspections of manufacturing facilities), Good Laboratory Practice and Good Clinical Practice. Bioequivalence needs to be verified for generic drugs that are supposed to replace a branded original. Bioequivalence is established through clinical tests in healthy volunteers, by measuring the blood levels of the drug substance over time and comparing them to the data obtained from the original product.

Low-income countries usually have no capacity to deal with the flood of data and information contained in a registration file for a new drug. Typically, the maker or importer of a drug has to provide documentation that the product is approved by a competent and internationally accepted authority, or alternatively that it has been included in the WHO prequalification list (currently relevant mainly for HIV/AIDS and malaria products).[5] In addition, test samples have to be provided for lab controls to confirm identity between the product specified on paper and the actual product. Based on these two key criteria (approval by a competent authority and identity), marketing authorization is granted. Capacity to assess a generic drug file is needed if there is a national drug industry, as described in the paragraph above on middle-income countries.

Countries with very limited financial and technical resources: For imports of essential drugs, the responsibility for ensuring pharmaceutical quality can be delegated to selected procurement agents, in the form of a contractual obligation to make sure that all drugs that are imported adhere to international pharmacopeia standards. Marketing authorization for essential drugs could be granted on a generic basis, quoting the published standard monograph in (for example) the US or European pharmacopeia as a reference. Manufacturers or importers, who provide products under contracts with the official procurement agents, would only have to register with the authority. Then a marketing license could be issued for a specified product, and a responsible license owner identified.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an attempt to standardize registration requirements mainly for new drugs. Its members are the regulatory agencies from the EU, US and Japan and representatives of the industry, and there is a Global Cooperation Group that represents the rest of the world. This group enables

developing countries to comment on the process or obtain information about emerging standards.

Regional collaboration for drug regulation is an option that is institutionalized only in the European Union so far: EMEA is an EU-level agency that evaluates new drugs. If it reaches a positive opinion, the European Commission can issue a marketing authorization for all member states.[6] Similar collaborative approaches are emerging for example among the ASEAN countries and certain Latin American countries.

Keeping drug information current

Knowledge about medicines is continuously evolving, with new data on indications, side effects, interactions with other drugs being added to the original body of information over time. Therefore, drug registration and licensing has to be a dynamic process, with regular reviews to update the information provided to physicians and patients, and elimination of medicines that have become obsolete.[4]

This is usually done by:

- Requesting regular updates from manufacturers as a prerequisite to maintaining marketing authorization
- A legal obligation for the manufacturer to notify the authorities immediately in case of quality problems or newly discovered side effects.
- Collecting reports about drug side effects through the national health system, using standardized forms and procedures that are developed in partnership with medical and pharmaceutical professional societies.
- Constant review of drug safety information from all sources.

In order to protect public health, an emergency response system is required in case of quality problems or new side effects that make it necessary to:

- Change the prescribing information
- Issue a warning letter to the medical community
- Recall a batch that failed quality tests
- Recall the entire product
- Or even suspend or cancel the product license

It is also important that the administration is in touch with other agencies and the international scientific community. Expertise is needed to identify warning signals for emerging drug safety issues and assess their relevance in the specific national context.

Older drugs should be de-registered if they are not marketed or used anymore. For example, marketing authorization could be withdrawn after a certain period if the manufacturer does not apply for an extension, or if there is scientific consensus that a particular product has become obsolete.

Quality control in the market

Drug registration ensures that only a product that is effective and of good quality will get a marketing license. But this does not guarantee that the actual product shipped by the manufacturer is identical with the licensed product. Unfortunately, errors or intentional fraud have occurred in the past, leading to a significant amount of sub-standard drugs in circulation, especially in some low-income countries.

In tropical countries, heat or humidity during storage and transportation can affect the stability of the formulation or harden the tablet so that it does not dissolve appropriately or becomes chemically altered and ineffective.

Therefore, as part of the regulatory framework, a drug quality monitoring system needs to be established that regularly checks the adherence of imported or locally manufactured drugs to the registered specifications:

- at the level where they enter the market (customs, factory)
- and again at the dispensing level (drugstore, pharmacy). This level is of particular importance, because here it is possible to detect counterfeit drugs which in most cases are illegally imported and therefore escape controls at customs.

Regulating behavior of market participants

The quality and cost of pharmaceuticals are influenced by a number of market participants, such as manufacturers, importers, wholesalers, pharmacists, physicians and other medical and non-medical professionals who use or dispense medicines. In an unregulated environment, patients are exposed to business practices that may benefit providers but can lead to sub-optimal treatment and higher costs than necessary, because patients do not have the expertise to judge the quality and cost of the drugs they receive.

The regulation of pharmaceutical marketing and sales should include all market participants, define their roles and responsibilities and set and enforce rules for professional conduct based on a contractual framework (accreditation model). Areas that are typically addressed in such a framework are:

- Education and professional training
- Standard of facilities
- Standard operating procedures
- Marketing practices
- Documentation and reporting obligations
- Organizational oversight/governance.

Control of drug promotion is an issue of concern in countries with a significant market size and presence of local or importing companies trying to “grow the market” and increase their share. Drug promotion and

advertising should adhere to certain standards. It should be reliable, accurate, truthful, informative, balanced, up-to-date, well substantiated and in good taste.[1] Some regulatory agencies retain the right to review and approve marketing materials and messages. This is labor-intensive and requires a significant investment in qualified staff. Another possibility is to ask the industry to develop a marketing codex based on international standards, together with an enforcement mechanism. To make this kind of self-control work, external verification and effective sanctions are required. These should be applied and controlled by an independent body, for example a committee that represents professional and non-professional stakeholder groups.

Institutional and organizational arrangements for drug regulation

Regulation of the pharmaceutical trade is a complex field, involving many players and disciplines. This is reflected in the legal framework, which is usually built around a food and drug act, complemented by several other pieces of legislation that regulate trade, industrial development, accreditation, pricing, promotion, prescribing and other aspects. The organizational integration of all these aspects is important. This can be done by a standing committee, which looks after all aspects of pharmaceutical policies and coordinates decisions and initiatives, which then are implemented by the responsible ministries and administrative bodies.

Useful Links

WHO drug regulatory support

<http://www.who.int/medicines/organization/gsm/activities/drugregul/orgdrugregsup.shtml>

WHO prequalification project:

<http://mednet3.who.int/prequal/>

European Medicines Agency on GMP:

<http://www.emea.eu.int/Inspections/GMPHome.html>

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) <http://www.ich.org>

World Bank support:

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