

Personal Perspectives

Risk assessment as an element of drug control

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The responsibility of governments to establish systems which assure that all pharmaceutical products used in a given country are both safe and effective is now generally accepted, even if the extent of such responsibility may differ between countries. The operation of such systems may be supervised by a special department within the Ministry of Health or delegated to a drug regulatory authority. In either case, such activities are carried out in close collaboration with those parties involved in drug manufacture and distribution, including manufacturers, wholesalers, hospitals, retail pharmacies and other drug distribution outlets.

The main purpose of a drug regulatory system is to prevent the occurrence of harmful drug related events which may have the potential to attain catastrophic proportions. Because of the need to maintain public confidence in pharmaceutical products for the general health of the population, a system of government-imposed regulations is often in operation, while responsible institutions and enterprises endeavour to ensure that no harmful negligence occurs during manufacture, distribution and use of medicinal products. Such additional activities ensure that all precautions are faithfully implemented by all those involved.

Medicines have important consequences for health and their regulation may involve decisions with international implications. As such, the advice of WHO in relation to these issues is considered highly relevant. Drug regulatory systems operate within the economic environment of the country as a whole and the level of development differs enormously between countries, with regard to the particularities of the restrictions encountered.

Drug-related hazards

While harmful events and risks are inherent in the nature of drugs, many risks can be avoided or at

least minimized through implementation of effective preventive measures. For the purposes of the present article, three types of risk may be distinguished.

1. Risks related to the introduction of new medicines

Risks related to the introduction of new medicines are linked to the possibility that an unknown harmful effect of a new substance will appear when the product is used extensively in the general population. Elaborate systems have now been developed for the prevention of such risks based on early detection of harmful effects in the course of pre-clinical testing or during clinical studies. Separate sets of requirements are established for new chemical entities and for new products obtained from biotechnology where additional kinds of risks can be expected. However, even highly elaborate systems cannot be completely foolproof, as is evidenced from cases where rapid withdrawal from the market of recently approved products was necessary (1).

2. Risks related to drug production

Risks that are related to the production of drugs include events resulting from improper manufacturing processes or cases of mix-ups and mislabelling during production. This type of hazard is not related to the intrinsic pharmacological property of the active substance or excipient but to the manufacturing process. Improper production includes the use of inadequate (substandard) starting materials as well as deficiencies in the technological processes of drug formulation. Such deficiencies could result, for example, in the manufacture of products of inadequate bioavailability, or may lead to the appearance of unexpected contaminants in the final product.

Risks related to the use of incorrect starting materials may have serious adverse consequences, as in the well-known cases of ethylene glycol being used in place of glycerol or as an admixture to an excipient (2). Similarly, the risk of contamination by adventitious impurities has also to be considered in the case of starting materials. Risks related to mix-ups may also occur within the drug distribution chain if re-packaging or re-labelling of products is

undertaken by traders, wholesalers or at retail level. Fraudulent production of counterfeit or adulterated drugs is a serious problem which should be considered separately (3). This criminal activity is linked to immense health risks.

3. Risks related to improper use of drugs

The improper use of drugs may lead to scenarios where harm is caused instead of expected relief. This includes mistakes made by physicians in the selection of drugs, irrational prescribing, over-prescribing (leading to over-consumption, particularly of antibiotics) (4), mistakes by auxiliary staff when administering medicines, lack of patient compliance, or mistakes made when taking medication. Some of those situations may also be created by unethical promotional practices which influence prescribing and consumption decisions. Effective drug information and education is essential to counter such practices. It is debatable to what extent drug regulatory authorities are able to take remedial action, since rational prescribing is primarily the responsibility of institutions which supervise medical practitioners.

Drug regulatory authorities

There have been few attempts to establish a classification of drug regulatory authorities into specific groups, although the notion of a small drug regulatory authority has been introduced by the WHO document *Guiding Principles for Small National Drug Regulatory Authorities* (5). The three following levels of drug regulation were identified in a recent report on global harmonization of regulatory requirements of pharmaceuticals (6). These categories often reflect the degree of economic development of countries, which confirms that the importance of economic factors in the health area extends also to drug regulation.

1. A sophisticated level of drug regulation

Countries with sophisticated drug regulatory activities are generally well equipped to prevent most types of risks related to medicines. Appropriate drug regulatory institutions exist to confirm the safety and efficacy of new drug entities. The majority of these activities are now carried out according to guidelines established by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). A brief review of ICH activities was recently published in *WHO Drug Information* (6).

High-income countries with sophisticated drug regulatory activities have properly functioning

systems for the establishment of drug quality requirements. This will include activities of pharmacopoeia commissions and well established surveillance systems on the manufacture and distribution of pharmaceuticals such as pharmaceutical inspection and national drug control laboratories. All institutions function effectively in order to reduce to a minimum the risks related to drug production and distribution.

Administrative regulations related to the introduction of new medicines and control of drug production can be properly implemented in high-income countries because the pharmaceutical industry, to which they are addressed, is well developed and drug distribution services are staffed by fully qualified personnel. Full implementation of the rules of good manufacturing practices (GMP) is also much simpler in facilities with high manufacturing standards and having at their disposal well-equipped and well-staffed analytical laboratories. The same can be said of institutions providing information on drug use for health professionals and the general public.

2. Drug regulation at the intermediate level

The medicines control situation is less sure in countries at the intermediate level. Countries in this group rely heavily on the evaluation of new drug entities carried out in countries with a sophisticated level of regulatory activity, avoiding, to some extent, the risks associated with unexpected harmful effects of new medicines. However, as the main source of pharmaceutical products will normally be the domestic manufacture of generic pharmaceuticals, the main risk encountered is that related to production processes.

Because of the country's economic situation, drug regulatory authorities have only moderate financial means at their disposal. Activities are mainly based on the use of national resources, not on outside aid, even if a measure of external advice is usually available. Local pharmaceutical manufacture in the majority of countries in this group, with a few notable exceptions, is based on the importation of raw materials, which gives rise to particular kinds of risk. Furthermore, the technical equipment of local pharmaceutical enterprises may be more rudimentary in comparison with pharmaceutical manufacture in the high-income countries. Drug distributors may also be more moderately equipped. Some countries in this group are also victims of fraudulent production of adulterated drugs. There is, therefore, a whole range of combinations of risk areas within drug regulation that exists in countries of this group.

3. Inadequate drug regulation

Countries with inadequate regulatory activity are quite numerous and comprise nearly all low-income countries where there is no infrastructure for regulatory activity or, where such infrastructure does exist, it is too weak to achieve effective regulation.

Typically, there is little local pharmaceutical manufacture, the drug distribution chain is only moderately equipped, while conditions at drug retail level can be described as quite rudimentary. These countries, using mostly imported pharmaceuticals, are highly vulnerable to risks that can occur during drug distribution including fraudulent distribution of adulterated drugs. As countries in this group are not able to create independent, effective drug regulation, they require strong external assistance.

The influence of drug risks on control strategies

As an intergovernmental institution responsible for all matters related to health, the World Health Organization provides advice to its Member States from both the international and national perspective. This is carried out through recommendations and suitable documentation for implementation by countries. Such advice is intended for global application and has been founded on an underlying notion that similar approaches can be applied all over the world in many health related areas. Such a notion also includes issues concerning drug regulation. This integral approach has gradually become diffused through the creation, for example, of essential drug programmes intended primarily for low-income countries. Furthermore, countries at different levels of economic development have become more and more conscious of the various types of risks inherent in providing medicines to their populations.

The lack of proper evaluation of potential hazards and the effectiveness of administrative counter-measures remains a serious obstacle for the selection of an appropriate strategy. Data collection that could help such evaluations is poorly organized, if it exists at all, and is further complicated by the need for greater transparency.

Control strategies of high-income countries

The activities of drug regulatory authorities in high-income countries are directed towards prevention of all types of risks, both those relevant to the introduction of new medicines and those that can occur during manufacture and distribution. To maintain a

sophisticated level of drug regulation, considerable financial outlays are necessary from governments and the pharmaceutical industry with the result that risks related to the production of drugs and drug distribution are kept at the lowest level. Major activities are now focused on a comprehensive maintenance strategy of prevention of hazards linked to the introduction of new medicines. Consequently, less attention is being paid to risks linked to drug production and distribution since this was achieved at earlier stages of development.

Control strategies for other countries

Unfortunately, the favourable situation existing in high-income countries does not exist in countries where risks linked to the production and distribution of drugs remain a problem. It may even be that the situation is becoming worse — in part due to the presence of counterfeit products. Appropriate advice is needed from WHO because, for economic reasons, a direct transposition of institutions and procedures which operate in high-income countries is not possible.

In countries at an intermediate level, the operation of drug regulatory institutions is reflected by national resources rather than outside aid operating within the constraints imposed by the economic situation of the country in question. In countries at medium and low-income level, such constraints are much more restrictive than those existing in economically developed countries. In such circumstances, to be fully effective, activities should be oriented where the risks are highest. The assessment of risks is therefore of primary importance in establishing effective drug control strategies.

Assessment of risks linked to the production of drugs should be based on a separate review of each of the main elements of the drug supply system as follows.

- local manufacture;
- sources of raw materials;
- production facilities;
- importation;
- products in final containers; and
- products to be repackaged and re-labelled.

Existing literature on quality assurance of pharmaceuticals, which includes numerous WHO documents, describes in detail the activities related to drug quality assurance in respect of each of these elements. The advice given in that literature is fully appropriate in a situation where adequate resources are available. What is usually missing, however, is a listing of priority risk areas to be considered in cases when insufficient economic resources do not permit a full implementation of all recommendations.

Alternative control strategies

An assessment of individual risks related to specific products and raw materials, and recognition of hazards at specific stages of production or distribution would permit national regulatory authorities to better plan a drug control strategy and render its activities more effective within available resources. The main element to be considered is the extent of reliance on documentary evidence concerning the quality of products against confirmation of their quality (identity, purity and strength) through testing of samples. This applies equally to preparations and to raw materials, either of domestic or foreign origin.

Documentary evidence is much cheaper to procure, but it confirms nothing more than the results obtained by the manufacturer's analytical laboratory at the time the product was released onto the market. Obviously, it requires an additional assurance that it indeed pertains to the product in question. A confirmatory testing of samples is much more expensive, as it requires the maintenance of a suitable testing laboratory added to the costs of analysis. Such confirmatory testing is therefore only carried out on a random basis. None the less, testing of actual samples taken from the market can confirm whether regulatory authority action is adequate and it will remind the manufacturers and importers of the existence of control. A proper combination of the two approaches should also take into account the specificity of risk situations, examples of which are given below.

In many countries, local manufacture of pharmaceutical preparations is based on imported raw materials, both for active materials and excipients. Assurance of the identity and purity of these materials can be based either on certificates of analysis issued by the manufacturer or trader, or on the results of confirmatory testing done locally by the manufacturer of the pharmaceutical preparation. When such confirmatory testing is done locally, the size of the consignment is of importance as in most

cases raw materials are shipped in a number of containers, not a single one. The risks that may occur here include those due to natural deterioration of the substance, to mix-ups caused by mistakes in labelling of containers or to contamination of the material by foreign substances. Such presence of adventitious impurities may occur by accident or may be intentional.

When assessing the level of risk of an individual substance, numerous factors have to be considered: the stability — intrinsic properties, or improvements made by the use of stabilizers or adequate containers; price of materials — expensive substances are particularly the target of fraudulent activity; and any other possible dangers related to use. The high-risk category also includes such deceptively innocuous substances as polyols (e.g. glycerol), where mix-ups or inept use as excipients have, as already mentioned, been the cause of many tragedies (1).

Requirements concerning production facilities and processes are the subject of recommendations related to good manufacturing practices (GMP). The assessment of risk is also needed here to indicate those elements of the production process where mistakes can have the most harmful consequences. For example, the risks related to mix-ups are the highest during the labelling stage, while the risk of cross-contamination (but also of mix-ups) is highest at weighing areas. Risk assessment should also take into account the type of products that are manufactured in a given production facility.

Situation of low-income countries

The existence of countries with insufficient drug regulation is an unfortunate situation which has been deplored by many authors (6). In such countries, the prevention of risks cannot be achieved through local efforts and appropriate strategies have to be developed to draw on outside assistance. This is especially valid in relation to imported pharmaceuticals on which these countries are usually heavily dependent. In the case of donated products, the assurance of quality should be the responsibility of the donor organizations. The use of certificates issued according to WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is a possible solution and special procedures exist also for assessing the acceptability of vaccines for purchase by United Nations agencies. Unfortunately, low-income countries are also highly vulnerable to risks related to counterfeited products.

Conclusions

Recognition of the risks that may occur in the drug area is fundamental for the establishment of effective preventive strategies. Although some risks are inherent in the utilization of pharmaceutical products, the majority of such risks are avoidable. 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, where more limited resources are at the disposal of regulatory authorities, the assessment of risks and designation of high-risk products, areas and situations will be a priority in designating priorities for control measures. WHO recommendations on drug regulatory and control activities should indicate, to the extent possible, the level of risk linked to specific elements and stages of the production and distribution of pharmaceuticals as this could improve the modalities of their implementation in practice.

References

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