

# Quality Assurance Issues

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## The importance of analytical procedures in regulatory control

*Thomas Layloff  
Division of Drug Analysis  
United States Food and Drug Administration  
St Louis, MO, USA*

A regulatory authority responsible for the quality of the pharmaceutical products distributed within its jurisdiction is confronted with many challenges in its efforts to assure the public health of its citizens. One of the primary tasks of regulation is to determine which products can safely be allowed onto the market. This is usually accomplished through a drug registration system.

The laboratory resources needed to support the regulation of any given market will depend heavily on whether or not the products are manufactured within that market area or whether they are largely imported. Consequently, if the market is important and handles large quantities of products, the official laboratory will need sufficient resources to provide an analytical service which will assure the quality of these products. This is especially important when products proposed for entry into the area have been manufactured in facilities which have not had direct inspection for compliance with good manufacturing practice (GMP).

In many developing countries, however, an unfortunate combination of two factors exists. On the one hand, there is a predominance of imported finished products and on the other, a lack of adequate analytical services. Product quality can be better assured if an inspection force is available to periodically visit manufacturing sites and review production records. Although the United States market is supplied mainly by manufacturers operating within its borders, the number of finished dosage forms entering the country is steadily increasing. It is furthermore expected that the current globalization of the pharmaceutical market will also give impetus to increased trading in finished dosage forms and this situation will demand even greater efforts by inspection and laboratory services.

Once drug registration has been established, compliance of the approved products with quality standards must be sought. In some instances, where a country depends largely on imported finished products, a regulatory authority will apply the same methods of analysis and quality standards as those in the country of product origin. Since little harmonization has so far taken place among the major pharmacopoeias, this could give rise to a situation where several different quality standards and methods of analysis are in use for the same product within a given country or market area.

The multiplicity of standards and methods applicable to the same product can result in an extremely complicated situation for the regulatory control services, such as the need to have access to each pharmacopoeia and the specific equipment and reagents used in the country of origin. In an effort to remedy this situation, it has been suggested that the establishment of a unique analytical monograph for registration purposes and an accompanying quality standard for each finished dosage form would help to ensure that the approved product conforms to the same standards. However, this undertaking would constitute an immense task, and an easier solution may be the adoption of specific monographs and quality standards for each approved product based on existing pharmacopoeias.

When a pharmaceutical product is received at a port of entry, it is subject to controls to determine its marketing status, labelling, and claimed ingredients. These determinations should be made on all products entering the market area. In order not to hold up shipments, analytical tests to substantiate the claimed product characteristics are needed rapidly and as near to the port of entry as possible. However, this is not always possible, since a market area can very often be serviced by multiple ports of entry and standard laboratory services are not necessarily available at all of them. In this situation, a preliminary screening can be made of the product to ascertain the presence of the active ingredient and the claimed amount. In order to be effective, this analysis must be carried out before

release of the goods. If this is not the case, the products will be distributed throughout the country and regulatory controls would be ineffective in the event that a product needs to be withdrawn. An array of chemical methods of analysis are available to provide information on the quality of a product and ensure that it complies with the regulatory requirements in force. This availability is, however, dependent on many factors such as funding and the extent to which these services are required. Consideration must additionally be addressed to sources of funding for staff, training, equipment, maintenance, supplies and running costs.

A preliminary screening at a port of entry will provide information on whether a product is approved for distribution, is properly labelled, contains the correct ingredient in the claimed amount and complies with legal specifications. It is at this point that counterfeit products can most conveniently be identified. Screening techniques include WHO basic tests, and other simple test methods. However, the use of thin layer chromatography (TLC) has been shown to be particularly useful during this preliminary screening phase. The tests are cheap and quick, require a low capital investment and have low operating costs. TLC requires minimum laboratory resources and analyst skills, which means that competent personnel can be easily trained in their use. Any sample found to fail the necessary tests using this method could then be subjected to analysis according to the legal reference methods (LRM) carried out by the regulatory control laboratory. Notwithstanding the simplicity of the method, TLC is reliable enough to support decisions on whether entry should be denied for products which fail significantly.

Once a product has entered the market and has been distributed, it falls within the jurisdiction of that market. This generally means that any regulatory action taken against the product must be based on LRM as determined by legislation. Thus, in addition to providing preliminary screening of imported products, regulatory authorities must maintain, or have access to, facilities suitable for conducting LRM which will confirm or refute the preliminary screening results. These facilities are also useful for carrying out special surveillance activities. Preliminary screening, with possible confirmatory LRM activities, is therefore essential before a product can be released into the market area, and to ensure that the product will comply with the claimed expiry date and required quality standards.

Unfortunately, in the case of the LRM, several days or weeks may be needed to set up the analytical equipment and prepare the reagents. In addition, many LRM use liquid chromatography (LC) or gas-liquid chromatography (GLC) methods. *The United States Pharmacopeia*, for example, contains over 800 monographs requiring LC and 150 monographs requiring GLC. As can be imagined, equipment for this type of analysis requires a relatively large capital investment, with the related costs for trained operators and maintenance staff. In the United States, a high-performance liquid chromatograph will cost approximately \$25 000 to \$65 000 depending on the accessories and attachments, and a gas-liquid chromatograph will cost between \$15 000 and \$70 000, although less expensive equipment may be available in other regions of the world. In order to keep the equipment operational and to replace worn parts, a laboratory will need an additional 5–10% of the initial cost for maintenance. It is important to have easy access to parts and circuit boards in addition to the necessary reagents, reference standards and supplies, the cost of which may represent a further 5–10% of the initial outlay. Furthermore, operation of the equipment can be affected by environmental factors such as temperature and humidity.

Experience with running an LRM facility suggests that, in order to be efficient, it should be equipped and staffed at a level over and above minimum requirements and it is often preferable to have three or more units of identical equipment so that aberrant results can be confirmed by a second apparatus. Also, modules can be switched around or exchanged when defective parts are identified. Multiple units of identical apparatus will also reduce the need for space to house spare parts and consumable supplies required to keep the equipment operational.

The acquisition of expertise is also an important factor if the laboratory is to be run successfully. In contrast to the minimum skills needed for applying the preliminary testing methods, personnel carrying out LRM need higher levels of training. In the more complex laboratory environments, it is useful to have several persons skilled in the same techniques working together in order to stimulate the functioning of the laboratory and discuss details of the work. This strengthens the analytical capability of the services provided and assists in the application of the more complicated instrumental techniques.

Because of the costs involved, LRM testing can only be performed on a fraction of the products actually in circulation and in many cases this is below 1% of the total. For example, in a country where 35 000 prescription-only medicines and 115 000 over-the-counter products are on the market, there would be 150 000 batch samples to be collected and analysed. For each product, analysis would include assay, content uniformity, release rate and identity and an approximate total of 30 analytical results would eventually be produced taking approximately one week per sample to complete. For the sake of statistics, it may be worth while for a regulatory authority to collaborate with industry in estimating the number of batches manufactured annually within the territory in order to compare these figures with the number of batches tested for compliance.

In some special cases, a product may need further testing using advanced analytical methods. For example, in the case of an epidemiological aberration associated with a specific product or in detection of counterfeit or spurious products. These methods will also provide a means of verification of the techniques proposed by manufacturers in the registration dossiers and may assist in carrying out research into detecting unexpected impurities, undeclared or substituted excipients or other characteristics which need examination. In this case, mass spectrometric, nuclear magnetic resonance, or X-ray powder diffraction analysis may be required. This can only be carried out by skilled staff backed by an armamentarium of sophisticated equipment normally available only at universities and research institutes. Access to this expertise should be facilitated whenever possible by the authorities.

It is therefore important that the regulation of pharmaceutical products in every country should include responsibility for the quality of products

circulating within its boundaries and those entering the market area from other parts of the world. This can only be achieved through a three-tiered system of preliminary and legally required methods (LRM) backed up by advanced analytical methods. This will enable large numbers of products to be screened to ensure identity and content amount, with an LRM level to validate the results of these techniques, confirm marginal findings and determine conformity with legal requirements. Advanced analytical methods will be relied on when sophisticated counterfeit products need to be identified or to confirm or refute circumstances of product-related, epidemiological events.

#### Further reading

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