

## General Policy Issues

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### Generic drugs: the hidden issues of quality and cost

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As we move into the new century, a widening economic gap separating rich and poor countries confronts the public health sector. The challenge lies in providing an acceptable level of health care at a reasonable cost for populations in the developing world — including the ever growing number of displaced communities — who are left behind in the economic race. Although the manufacture of generic essential drugs offers a practical way of achieving this aim, the quality of these products tends to be jeopardized by overriding considerations of cost. Assuring the quality and safety of essential drugs is paramount to achieving effective implementation of national drug policies, pharmaceutical programmes and humanitarian relief operations (1).

Quality assurance of medicines is a feature of all procedures and processes employed throughout the production chain: whether development, manufacture, monitoring, distribution or final use. Unfortunately, it is not possible to evaluate the quality of products merely through the provision of a compliance certificate for good manufacturing practices (GMP) or from the results of a quality control test. The specific criteria of quality control each confirm the validity of different stages of manufacture and process control points. Quality thus has to be built in at each critical stage of the production process, the end result of which is the production of a medicinal product fit for its purpose and use (2).

Regulatory information reflecting the manufacturing status and provenance of imported medicines, such as that provided through the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, is essential but will only be of use if the drugs are approved for marketing in the country of origin. Developing countries should also evaluate their own particular needs and standards in relation to the national and international situation. International open tenders may seem to offer the advantage of favouring competition and increasing the possibility of access to essential drugs by lowering the price, but the principal drawback to this option

is that quality is not always given the priority it deserves over cost considerations.

The WHO Model List of Essential Drugs and the underpinning concept were developed in the 1970s to stimulate the rational availability of medicines in developing countries. Essential drugs are those that meet the health needs of the majority of the population; they should be available at all times in adequate amounts and in appropriate dosage forms. The WHO Model List of Essential Drugs enables countries to identify priorities and make their own drug selection.

The term generic drug has been legally defined in France as "a copy of an original medicinal drug whereby production and marketing are made possible by the expiry of the patent covering the innovator product" (3). It is further described in the Public Health Code as "a specialty which is essentially similar and presents the same qualitative and quantitative composition of active ingredients, the same dosage form, and bioequivalence as the original product" (4).

In the manufacture of generic drugs, the three concepts of quality, safety and efficacy apply to generics in the same way as they do to the innovator product. Regulatory authorities should require that documentation supporting a generic pharmaceutical product meets the following criteria:

- manufacture (GMP) and quality control;
- product characteristics and labelling; and
- therapeutic equivalence.

Reasonable assurance must be provided that the generic drug is clinically interchangeable with the nominally equivalent marketed product (5). When the therapeutic activity of the active ingredient is known and correctly reproduced, clinical studies are unnecessary although bioequivalence data will be required. Safety data are provided through reference to the literature, and can be supported by a profile listing impurities and degradation products and stability studies. It is clear that such principles will be meaningless if quality raw materials are not used: whether as active ingredients, excipients, accessory materials, manufacturing intermediaries or primary packaging.

For a generic drug, the quality of the active ingredient takes on great importance. Almost 90% of essential drugs contained in the WHO Model List are off-patent and available in generic form. Raw materials can also be generic, and their cost can vary considerably depending on

labour costs, quality of the facilities, reputation of the supplier, quality and purity processes applied to the material. Professional judgement must be exercised in the purchase of such materials because compliance with pharmacopoeial specifications may not necessarily indicate good quality. The price of the raw material often represents more than 50% of the industrial cost price of a generic, which may lead manufacturers to target a lower quality raw material in their efforts to offer competitively attractive prices.

### **The quality of raw materials**

The quality of the raw material is unfortunately a parameter that is rarely taken into account in granting export permits for generics if they are not licensed for sale on the domestic market, and rarely is this parameter considered important by international purchasers.

Equally, the method of drug synthesis is an important consideration which will enhance the quality of the drug. Pharmacopoeial monographs are based on the latest synthesis procedures where impurities, related substances and subproducts of degradation are well defined. A change in the method of synthesis must therefore be followed by a suitable adaptation to the process control, which is not always the case. The purchaser of generic drugs should be aware that conducting analyses which rely solely on pharmacopoeial monographs may not necessarily indicate the risk of toxicity from degradation products or impurities in the event that the method of synthesis has been changed (1).

The raw material market is extensive and a great choice of products is available worldwide. The following quality problems may be encountered when suppliers are located in different parts of the world:

- Geographical distance makes it difficult to locate or get information on the actual suppliers. The practice of using brokers or commercial intermediaries to facilitate administration and communication tends to break the bond between supplier-client. Additionally, a broker may be dealing with several manufacturers who are providing different components of one finished product.
- It may be difficult to locate the manufacturer of the raw material and obtain details of the synthesis procedure (profile of impurities and degradation products).
- Even when the manufacturer is known, distances make it both difficult and costly to audit.
- Production may be held up if suppliers are changed, if a source is suddenly cut or if the raw material is of a different standard and requires adjustments to the product formula.

Greater vigilance is therefore needed to assure quality when suppliers are situated at great distances. None the less, some countries have good systems and testing facilities in place.

### **Excipients**

Since excipients often make up the bulk of a formulation, the same requirements and quality criteria should apply. The great diversity and use of excipients throughout other industries makes it of paramount importance to establish their purity and chemical and pharmaceutical quality. Tests should include a rheological study, solubility and kinetics of dissolution, determination of specific surface, establishment of a granulometric curve and shredding.

Any change in the excipient may cause variations in bioavailability and produce toxic phenomena or allergies. Several examples of such variations have been encountered with fatal consequences for the patient. Recommendations on the control and safe trade in starting materials for pharmaceuticals have been published by WHO (6). Certificates of analysis and vendor qualification should comply with guidelines of the International Pharmaceuticals Excipient Council (IPEC) (7).

### **Packaging/containers**

It must be remembered that the container will also come into direct contact with the pharmaceutical product. Careful consideration should therefore be given to the material and composition of the container.

The manufacturer must clearly communicate medical grade specifications because the supplier of the container does not necessarily know the level of quality requirements.

In tropical countries, plastic containers, for example, may not be recommended due to interactions between container/content or between powders and container walls. Adsorption of plastic materials will also modify the stability of the product. Intolerance reactions or toxic phenomena can result from the stability modifications of the product following a shift in content constituents and adherence to the sides of the container.

### **Stability studies**

The stability of a drug is evaluated through its ability to maintain chemical, physical, microbiological and biopharmaceutical properties within specified limits during the entire extent of its validity. There are two types of stability studies (i) accelerated degradation studies meant to increase the speed of physical or chemical degradation of a drug by subjecting it to extreme storage conditions and (ii) stability studies in real time. This would be an experimental study of the chemical, physical, biological and microbiological characteristics of a drug during its period of validity, foreseen use and beyond, under real storage conditions as encountered in the market for which it is intended.

Tests for high humidity conditions are particularly important because the risk of degradation of semipermeable packaging is much higher. Evidence of stability studies is one of the most important parameters to be considered for supplies because:

- climatic conditions in many developing countries are very different to those in temperate climates which serve as a reference for studies.
- poor stability may lead to drugs becoming toxic or increasingly inactive.
- stability cannot be evaluated through quality control of the delivered final product.

### **Bioequivalence**

Bioequivalence refers to the speed and absorption by the body of the pharmaceutical, the active principle or its therapeutic fraction. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and if the rate and extent of availability after administration in the same molar dose is essentially the same. Different methods may be used to demonstrate this:

- comparative bioavailability studies in humans consisting of titration of the active ingredient or one or several of its metabolites in an accessible biological liquid such as plasma, blood or urine;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials; and
- in vitro dissolution tests.

### **Means available to evaluate drugs**

In many developing countries, central purchasing depots have been created and rely on a system of open tendering. However, if this allows drugs to be obtained at a very low price, it does not address the need for quality products. Further shortcomings to this kind of method include:

- numbers of suppliers in all countries worldwide will respond to open tenders.
- there is a lack of quality control laboratories in developing countries. Where these are present, they suffer from underresourcing in staff, material and finances.
- a large proportion of drugs on open tender do not have a marketing authorization in the country of manufacture.
- even if drugs do have a marketing authorization, the requirements for authorization may differ between countries. Furthermore, a product may be marketed in packaging which will change when supplied in bulk to developing countries or humanitarian aid programmes. For example, products which are supplied in 28-day patient packs with information leaflets are supplied in bulk packs of maybe 1000 tablets.
- export certificates may not conform to the requirements of the importer and verification of the file with the actual

practices of the manufacturer are almost always precluded.

Three approaches are available for the evaluation of drugs:

1. Proof of quality control at various stages, i.e. receipt of raw material, in-production process, and finished product.
2. Audit of the manufacturer to include process validation of manufacturing and quality assurance.
3. Registration of the drug in the country of manufacture and in the importing country. Where a product is not for local use, the registration authority must ensure that the same laws and regulations which apply to the manufacture and sale of products on the local market also apply to products to be exported/imported.

An association of these approaches will strengthen the objectives of providing quality drugs at the lowest price.

### **Hidden cost**

Most buyers of healthcare and medicinal products will be aware of the usual implicit hidden costs such as freight costs. Experience will urge them to ask for a quotation of these costs to be included with the goods to be purchased. These basic costs should be included as part of budgeting and forecasting of need.

One ambivalent hidden cost is that of purchasing poor quality medicinal products. Suppliers offering the lowest prices often win the tender, particularly where the country is self-financing, or is directly controlling donated funds. Although there is always a desire to stretch the funds to cover as wide a need as possible, this should not compel buyers to forego the important issue of product quality. Poor performance of procured drugs is not just costly in financial terms, but in the number of patients who may be affected by consuming poor quality or ineffective products. It is important that buyers are aware of the wider implications of their function: that of saving human lives and not just saving money. If goods are purchased from suppliers and manufacturers with a validated track record, this would guarantee safeguards which low-cost suppliers are unable to provide.

### **Proposed strategy**

The first step should be to avoid calls for open tenders, even where stringent guidelines are in operation, and to prefer limited calls for tenders from a restricted list of prequalified suppliers (1). In this event quality assurance factors would apply equally to distributors and manufacturers.

### **Safety and quality assurance**

A systematic audit of the manufacturer should be made through documentary evaluation via the site master file or effective auditing according to GMP. This must stress

process validation and competence to manufacture products fit for their intended purpose.

### **Registration in the country of origin**

Any manufacturer not applying for a marketing authorization in the country of origin should nonetheless provide sufficient elements of the master file to complete an evaluation. The importing country should evaluate this file in line with its own criteria for bioequivalence, expected uses, medical information, labelling and sampling.

The exporting country should be able to assure drug quality through an evaluation of the information contained in the master file and be able to inspect the manufacturer on that basis. Furthermore, it should be the responsibility of the relevant authorities to ensure that there is a clear and qualitative difference between a manufacturing licence for medicines and healthcare products and the licence for non-medical products.

### **Mutual recognition of inspections**

Inspections should be promoted to ensure conformity with the reference data. Developing countries should be encouraged to adhere to the Pharmaceutical Inspections Convention (PIC) treaty.

In conclusion, quality assurance is an important tool in the control and evaluation of drugs. This is the only approach that can currently provide assurance that the product is safe for human use. However, this approach has a price and competition for supplies needs to take place among suppliers known to apply quality assurance procedures.

Furthermore, manufacturers must collaborate more fully with drug regulatory authorities to ensure quality when drugs are exported. This will ensure that drug quality in developing countries will be more standardized and rational.

If it is important to ensure that the demands made on manufacturers and suppliers of quality medicinal products are met, it is equally important that the authorities demanding the drugs accept the costs implied in assuring quality. It is a fallacy to believe that quality production and assurance can be achieved at no great investment. The following factors need to be understood in the drug procurement process:

- Quality has a cost;
- Procurement from non-validated suppliers carries a health risk for the patient;
- Cheap medical products also carry a health risk;
- Procurement should be restricted to selected suppliers, not through open tender;
- Suppliers should be validated according to a country's defined quality supply standards

- In the absence of local standards, use those promoted by WHO.

- Conformity with international standards, as promoted by WHO, should be demanded.

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