Editorial

Making medicines safe

Jean-Yves Videau[1]

During the last 15 years, several hundred patients, many of them children, have died worldwide[a] from intoxication after using medicines contaminated by diethylene glycol (DEG) (*1*). The latest outbreak — in Gurgaon, India — in 1998, is described by Singh et al. on pp. 88–95. Besides these dramatic outbreaks caused by the acute toxicity of DEG, a more general and often underestimated danger is growing, especially in developing countries: the rise in substandard medicines with concomitant problems of toxicity, instability and ineffectiveness.

The term "generic drug" has been legally defined 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. It is further described in the French *Code de la Santé publique* as "a specialty which is essentially similar and presents the same qualitative and quantitative composition of active ingredients, and the same dosage form and bio-equivalence, as the original product" (Décret 97-221, 13 March 1997).

Although generics are currently the only way of making essential drugs financially accessible to most of the world's population, in no case should their quality, effectiveness and safety be sacrificed. These three criteria are the cornerstone for health products, and they have to be demonstrated and verified. This is done when the drug is registered in its country of origin for its own market, and it is genuinely checked by experts of the national regulatory authority. The registration file for a generic has to include full information on the origin and the specific characteristics of the raw materials. If necessary, it should also provide proof of bio-equivalence and the results of tests demonstrating its stability in the climatic conditions where it will be used.

The situation becomes more complicated when the medicine is manufactured without registration and especially for export. In this case the WHO certification scheme will only call for data on the conditions of manufacture, checked for good manufacturing practices (GMP) by the national regulatory authority. Even when the drug meets the standards of GMP, the intrinsic references for its safety and effectiveness are still missing. When the licence of a drug expires, the active substance may be manufactured anywhere, and the process of synthesis, purification and crystallization may vary from place to place. The methods used to manufacture the active substance can therefore be different from those used as a basis for the tests described in the pharmacopoeial monographs. A basic fact of life in analytical chemistry is that one only finds what one is looking for. Thus in the absence of a Drug Master File (DMF), a European Drug Master File (EDMF) or a Certification of suitability of the monographs of the European Pharmacopoeia (CEP), one can completely overlook impurities which are present in the active substance. These impurities, introduced by other ways of manufacturing the active molecule, can play a significant role in the toxicity or poor stability of the final medicine. (*2*).

To avoid these difficulties, a manufacturer of medicines must possess all the details of the origin of the starting materials and a clear audit trail for them. Therefore every plant manufacturing such products intended for pharmaceutical use, as well as the active substances, excipients and packaging involved, should employ a suitable quality management system such as GMP or the ISO 9000 series, and be regularly audited and authorized (*3*). With such a system in place the incidents of DEG poisoning referred to above would not have happened.

Concerning the effectiveness of generics, besides the potential unknown impurities, the multi-source origin of active substances may lead to solubility differences arising from changes in crystallization characteristics (such as polymorphism, habitus and particle size) (*4*). Likewise, for each generic of one active molecule, the formulation and the manufacturing process may differ, leading to variations in bioavailability from one finished product to another.

The pharmacological activity of a generic active ingredient is well known. In the absence of clinical trials, the in vivo release kinetics of the finished product have to be taken into consideration. This means that in most cases, and particularly for oral generic forms, a bio-equivalence study against the innovator product will be required except when a single in vitro kinetic dissolution comparison is proved to be sufficient.

All these points have to be checked and established in order to guarantee the quality, effectiveness and safety of a generic. A medicine is not just a simple mixture of chemical ingredients, it is a very complex equilibrium with potential interactions and, in order to benefit the patient without any risk of harm, it needs an approach which is completely professional and responsible. Quality, therefore, has to be built in at each critical stage of the production process. All of the parties in the chain from the production of starting materials to the manufacture of the finished product have a responsibility for their actions which must be documented in compliance with established GMP (*3*). This chain of professional responsibility has to be continued to the end user, who is the patient, maintaining the same rigorous standards of pharmaceutical quality requirements throughout.

In addition to being responsible for the quality of their own link in the chain, all participants must check to ensure the quality of the product they receive from the preceding stage in the process. A country has to take responsibility for meeting the standards that are set nationally and regulated by international agreements. By applying these regulations, an importing country should be able to decide for itself whether a given product is safe. At the same time, however, it is easier to control the quality of a product at its origin; so, to help the importing countries in their choice, the exporting countries must accept full responsibility for the quality of the medicines they are exporting. ■

1. **O'Brien KL et al.** Diethylene glycol poisoning. *JAMA,* 1998, **279**: 1175–1180.
2. **Andriollo O et al.** The quality of essential multisource drugs. *STP Pharma Pratiques,* 1998, **8**: 137–155.
3. *Starting materials for pharmaceutical products: control and safe trade.* Geneva, World Health Organization, 1998 (unpublished document WHO/PHARM/98.605).
4. **Laloge M et al.** Incidence de l'origine des matières premières sur leurs qualités pharmacotechniques [The effect of the origin of starting materials on their pharmacotechnical qualities]. *STP Pharma Pratiques,* 1988, **4**: 319–324.

[1] General Manager, Responsible Pharmacist, Centrale Humanitaire Medico-Pharmaceutique, 63100 Clermont-Ferrand, France (email: jy.videau@chmp.org).

[a] 1985, Spain; 1986, India (Mumbai); 1990, Nigeria; 1990–92 Bangladesh; 1992, Argentina; 1995–96, Haïti; 1998, India (Gurgaon).

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