

No Safe Medicines Without Safe Ingredients

Today, it is accepted worldwide that quality and safety of medicines can be built-in only by applying a set of measures and controls during development and production - known under the term “GMP” (Good Manufacturing Practice) - instead of by mere end product testing. This principle applies equally to the active components of medicines (Active Pharmaceutical Ingredients = APIs).

European Authorities recognize the principle of GMP as fundamental, both for medicinal products and for their APIs. However, whereas they have established a tight net of direct enforcement measures by regular inspections of the medicinal products manufacturers, surprisingly they show reluctance to implement the same enforcement on the APIs for the same medicines and are leaving that responsibility completely to the discretion of the finished dosage form producers.

The European API industry association APIC appreciates the incorporation of the GMP principles for APIs into the European drug code. However, a “well-intended” regulation can easily result in the opposite effect if enforcement is not applied and control by the authorities would be absent. The number of API manufacturers increases rapidly and EU producers of finished medicines are subject to increased price competition. The European Commission must create conditions that will ensure that competition never leads to sub-standard medicines. Therefore, the need for action is urgent:

The downward pressure on pricing of medicines in Europe urges EU manufacturers to seek new, lower priced API suppliers. However, such lower prices can originate in part from lower costs because of sub-standard GMP- and regulatory compliance levels at the supplier. So the serious concern of APIC is that this is resulting in EU pharmaceutical companies - also partly without their knowledge - compromising on quality by sourcing from what appear to be sub-standard suppliers.

Worrying scientific data and other information on APIs that show substantial risks to patient safety in the EU have surfaced in the recent past. Examples are the Gentamicin case (ref.1) - giving strong indications that more than 33% of the gentamicin API material on the EU market was produced by unknown manufacturers and is therefore illegal - and the experiences shared by a recognized API trading company at a recent European API Conference in Lisbon (October 2004) (ref.2), showing that the traceability of API material back to the manufacturer is frequently lacking.

Consequently, the EU’s high standards of quality, safety and efficacy of its medicines, particularly in the highly competitive generic-, “me-too”- and OTC markets, are starting to be seriously undermined by current API trends.

Unless control over the API supply to the European market is drastically increased, API manufacturers throughout the world who are applying the strict and costly standards of EU regulations and guidelines will have a severe competitive disadvantage against less ethical companies: “Good” APIs and pharmaceutical firms will be pushed out of business by “bad” APIs and pharmaceutical firms.

In order to reduce the risk for the European patients and for the sake of the continuity of API manufacturers who comply with the regulations, the EU must create the legal framework for a uniform level playing field for all API suppliers to the European market based on:

1. A mandatory and effective inspection service that will verify if the API manufacturing processes and controls comply with the ICH/Q7A GMP Guideline and are in accordance with the information included in the respective CEP dossiers, DMFs or MAs.
2. A sampling program to assure quality surveillance of medicines and their APIs.
3. The compulsory requirement to include with every Marketing Authorization a current and appropriate Certificate of GMP compliance issued by the EU inspectorate to the producer of the API.
4. Periodic follow-up inspections to reconfirm the validity of the GMP Certificate.

These provisions will also ensure a better level playing field in the EU market for finished medicines, whilst also reducing operational costs (e.g. a single authority inspection may avoid the need for multiple client audits).

APIC, Sector Group of Cefic
24 December 2004

1. “Composition and Impurity Profile of Multisource Raw Material of Gentamicin – a Comparison”; Frank Wienen, Ralph Deubner and Ulrike Holzgrabe; Pharmeuropa Vol. 15, No. 2, April 2003:
http://www.gmpapi.migg.com/download/fqs11289_4400_15007.pdf
2. “Agents, Brokers, Traders, Distributors, Repackers and Relabellers Issues”, Karl Metzger, Welding GmbH & Co. KG., 7th European API Conference, Lisbon, 20 – 22 October 2004:
<http://www.gmpapi.migg.com/download/fqs>