

# Quality Assurance Issues

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## Good pharmaceutical trade and distribution practices

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Over the past sixty years, there have been over 500 reported cases of fatal incidents due to the accidental but also fraudulent incorporation of diethylene glycol into pharmaceuticals (1). About 80 children died in Haiti in 1996 as a result of contaminated paracetamol syrup containing diethylene glycol in glycerol used as an excipient. A similar case of diethylene glycol poisoning was identified in India between April and June 1999 (2). The *WHO Drug Information* has also published articles on other cases reported worldwide (3).

WHO has developed guidelines on good manufacturing practices (GMP) for both finished pharmaceutical dosage forms and starting materials (4), while other regulations and guidelines continue to be issued. A Guideline on Good Manufacturing Practice for Active Pharmaceutical Ingredients has also been approved by the International Conference on Harmonization (ICH) (5). Other bodies, such as the International Pharmaceutical Excipients Council or the United States Pharmacopoeia, have published recommendations (6–7). WHO Guidelines for the Manufacture of Pharmaceutical Excipients were published in 1999 (8) although no equivalent ICH guideline yet exists. Although high quality production standards will guarantee a good quality product, they do not confirm that high quality starting materials are indeed delivered to the pharmaceutical manufacturers.

Industry has engaged in a voluntary programme of responsible care and product stewardship, as set out on the following page. Such programmes should ensure that only safe products are used. However, the best programmes cannot defeat all fraudulent practices. Unscrupulous individuals concerned with making quick and easy money will continue to seek out any loopholes in regulations

and circumvent systems in particular when regulations are absent or not enforced (9).

## How do these products reach the consumer ?

When company A buys from manufacturing company B, does company A really receive a product made by company B? Hopefully, yes. But this is not always the case. The commercial practices described below are considered normal transactions in many countries and demonstrate the difficulties encountered in operating effective control systems.

- Producer A has more orders on the books for active ingredients than he can handle. Therefore, he orders products from company B to be delivered in neutral drums (no labels, or peelable labels). He will then relabel these drums with his own labels and reissue the certificate of analysis.
- Export company XYZ exports products bearing with its own labels, without reference to the original producer. Additionally, the company may source from several different producers at the same time.
- A distributor repackages a product in smaller containers under its own name, without traceability to the original producer. Such practice is also fairly common in some European companies which are not obliged to communicate the origin of the goods.
- A technical product or a food-grade product is re-analysed by the broker/distributor and found compliant with a given pharmacopoeia, and relabelled as being of pharmaceutical quality.

The above practices, and many more, have a potential impact because these products are eventually administered to humans for sometimes quite serious health conditions. In all the cases above, there is no way to guarantee that the product originates from a plant where appropriate GMP standards have been implemented. Absent cleaning validations, the use of low quality water, the use

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\*Authors alone are responsible for views expressed in signed contributions.

### PRODUCT STEWARDSHIP\*

- Product stewardship is the responsible and ethical management of health, safety and environmental aspects of a product throughout its total life cycle. Product Stewardship is Responsible Care® applied to products.
- Product stewardship improves market confidence. By defining and pursuing common goals throughout the supply chain, we can achieve benefits for all businesses involved.
- No company operates in isolation. Everyone involved in the production, handling, use and disposal of chemicals has a shared responsibility to ensure their safe management and use.
- By adopting a programme of Product Stewardship, every company can play its part in protecting humans and the environment from potential harm.

### WHY PRODUCT STEWARDSHIP?

- Every company, up and down the supply chain, should be concerned about the impact of chemicals on human health and the environment, throughout their life cycle.
- Each of us is confronted with a multitude of safety, health, and environmental issues regarding our products. These may be voiced by our customers, environmental groups, and regulatory authorities. They may arise from special expectations and public concern or from the industry's own internal assessment.
- Implementing Product Stewardship helps us to manage these issues more effectively, taking into account health, safety and environmental as well as technical and economic aspects to ensure best customer value.
- Chemical products must be managed and used safely along the supply chain, through manufacture, packaging, distribution, use and ultimate disposal.

\*The European Chemical Industry Council (CEFIC) definition,

of unacceptable solvents such as benzene, or process changes which go unreported and unvalidated, can result in unsafe medicinal products. Recent FDA warning letters indicate that some facilities who claim GMP compliance have never carried out the corrections they committed to make in writing. Are these exceptions to the rule, or are they the tip of the iceberg?

Furthermore, if there is lack of traceability, a variable or unknown origin of the goods, all process validation files of the medicinal producer are — by definition — meaningless, and this includes all the stability data. Processing conditions may vary depending on the source of the starting materials, which has a direct impact on bioavailability and hence on the efficacy of the medicinal product.

Another frequent observation is that products are being offered against obsolete pharmacopoeial

standards. For example, at the end of the year 2000, acetylsalicylic acid was reported to have been offered, with compliance stated against BP-80 although the British Pharmacopoeia monograph was changed in 1986 and again in 2000. The monograph change concerned related substances, suspected to be mutagenic and now limited at 0.1%. The samples of the product offered had over 0.2 % of the principal impurity.

These are not the only recurring fraudulent practices by far. Several constructions are known, often related to the registration process or patent infringement. A lot of money can be made by committing fraud, and the risks taken are sometimes significantly lower than those, for example, of narcotics dealers for which capital punishment is often the penalty. Yet fraud with medicinal products can be as devastating to the end user as narcotics!

### Supply chain characteristics of excipients

During the past decade, the excipient market has changed from a regional to a global market. Companies have become international, manufacturing products from only a small number of sites for the whole global market. New competitors have appeared, especially in Eastern Europe and Asia. This situation has led to a movement of excipients throughout the world. In this environment, distributors become more involved in the supply chain.

The incident in Haiti of contaminated paracetamol illustrates the extent and dramatic consequences of improper handling of excipients by supply chain brokers. Several distributors were involved in this incident, the product was shipped all around the world — from Asia via Europe to Haiti, with no traceability, insufficient controls and documentation lacking. Other similar incidents have also been reported (10).

In many countries, distributors are in charge of the excipients business because pharmaceutical companies have low consumption of these products compared to the large quantities used in food production, or for cosmetic and technical applications. Of course, some exemptions exist concerning particular excipients used exclusively for pharmaceutical applications. However, most distributors dealing with excipients are involved in trading to businesses with technical applications and often supply similar products for different uses. In these other business lines, processes involving mixing or minor cross contamination, are not viewed with the same precision as they are in pharmaceutical production. Traceability and documentation are not strictly required, nor do customers wish to pay for this service when using such materials for technical, food or cosmetic applications.

Given this situation, managing the distribution of pharmaceuticals requires sensitivity of the issues and knowledge of how to deal with the different requirements for the many similar products and their different applications. Incidents with contaminated excipients in the past showed that there is a lack of good practice in this area but no detailed regulation yet exists that provides standards for industry and regulatory authorities.

### Current legislation and guidelines on good distribution practices (GDP)

The latest harmonized ICH Guideline: Good Manufacturing Practice for Active Pharmaceutical Ingre-

dients (Q7a), approved in November 2000 includes a chapter entitled "Agents, brokers, traders, distributors, repackers, and relabelers". Within that chapter, special requirements for distributors are defined regarding traceability, stability, repackaging, transfer of information, complaints and recalls (5).

The French Medicines Agency (AFSSAPS) is currently preparing an exhaustive guide for good distribution practices covering both active pharmaceutical ingredients and excipients. This is still a draft working document, but it is likely to be published and implemented before the end of 2001. The International Pharmaceutical Excipients Council (IPEC) has also issued an audit-style questionnaire specifically designed for assessing distributors of excipients and is based on IPEC *GMP Guidelines for Bulk Pharmaceutical Excipients* (11). This document is intended to be used by pharmaceutical companies for auditing their supply distributors as part of their supplier evaluation system, as well as certifying distributors against IPEC standards. It should be used as a tool to assess the actual GMP/GDP level of distributors, to raise awareness and improve knowledge of supply chain actors, and thereby improve GMP compliance.

The European Association of Chemical Distributors (FECC) and other traders' organizations have also published a discussion paper entitled *GMP for Active Pharmaceutical Ingredients in Distributive Trade* (12). However, there is so far no final agreement amongst traders and brokers on these requirements and on the implementation of the principles set out in the document. Furthermore, there have been substantial comments made by some trader's organizations on the GDP requirements of ICH Draft Q7a, claiming that these requirements will lead to substantial price increases in Europe.

The European Chemical Industry Council (CEFIC) has published *Guidelines for Handling and Distribution of Propylene glycol USP/EP* (13) as part of their Responsible Care Program. The Guidelines were created by European manufacturers of propylene glycol USP/EP and contain relevant instructions and procedures to ensure safety and quality of propylene glycol from the manufacturing site down to the end user, bearing in mind special applications in pharmaceuticals, and consumer health protection measures. Similar ideas and strategies are included in the *European Single Assessment Document for Chemical Distributors* (ESAD), a document published by CEFIC and FECC in 1999

(14). In this document, specific guidance is given for the distribution of excipients, food and cosmetic ingredients. It can be used either by manufacturers to assess their distribution partners, or by customers to find out what level of GMP/GDP distributors of excipients have achieved.

### **Do these regulations suffice to safeguard public health?**

Maintaining quality standards and product safety has a price, but negating the need for requirements with purely commercial arguments is unacceptable when the implicit risks to human health are considered. The need for global recommendations and control is crucial: if the expense of applying quality and safety practices risks forcing the compliant companies out of business because they charge higher prices than their unscrupulous rivals, then this is obviously a horrifying prospect! It is possible that the current GMP practices dealing with active pharmaceutical ingredients (API), excipient trading and distribution are not sufficient to guarantee product quality and safety.

Several guidance documents require full traceability back to the original producers. However, a repacker or re-labeller is also often considered to be a manufacturer, so that traceability to the last "manufacturing step" is clearly insufficient. Other guidelines require a reference to the original producer on the certificate of analysis. The traceability requirement clearly needs to be bi-directional and is best reflected in section 17.60 of ICH Q7a which states: "Agents, brokers, distributors, re-packers, or re-labellers should transfer all quality or regulatory information received from an active pharmaceutical ingredient (API) or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer."

The API industry endorses these requirements. However, as long as there are no stringent verification and enforcement regulations in place, it is likely that fraudulent practices will continue to prosper. Europe intends to amend its Starting Materials Directive (75/319 EC) which will create a legal basis for the implementation of these GMP / GDP requirements. This will also create a legal basis for inspections covering manufacturers that are exporting products into the European Union, or intend to do so. However, in the current draft text of the Amendment, the decision to inspect is being left to the discretion of each Member State. Considering current budget restrictions in several countries, industry fears that substandard products, or prod-

ucts made by different processes to those declared in regulatory filings, will continue to enter into the European Union. This particularly concerns generics and over-the-counter (OTC) products, for which controls are minimal. OTC products are generally not even inspected, so similar concerns apply to imports of these products.

Recently, market prices of pharmaceutical ingredients for generics and OTC products have been forced to below economic levels. The inroad onto the market of products manufactured under inadequate — or even in the absence of — systems that should secure their quality and safety seems to be one important causative factor for this development. Omitting the use of such systems allows for lower manufacturing costs and therefore offers an important competitive edge. The implicit risks to humans are evident: such products are often sold to very large populations. For example, it is estimated that annually about 70,000 tons of paracetamol (acetaminophen) are consumed worldwide, representing a total of 150 billion tablets. A substandard product could have a more lethal impact than an atom bomb in such cases!

Similar requirements will certainly also be needed with regard to trade in pharmaceutical ingredients worldwide. The first steps that have been taken in this direction by WHO will hopefully lead to increased safety of medicines on a global scale.

In conclusion, the API manufacturing industry looks forward to presentation of a final text for Amendment of 75/319/EC for approval by the European Council and European Parliament. After all, it is the safety of patients which is at stake.

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