



**WORLD HEALTH ORGANIZATION
ORGANIZATION MONDIALE DE LA SANTE**

**STARTING MATERIALS FOR PHARMACEUTICAL PRODUCTS:
CONTROL AND SAFE TRADE**

Geneva, 25-27 May 1998

REPORT

1. Introduction

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. This includes the quality of starting materials, including active substances and excipients, for the production of medicinal products. For the purposes of this report, packaging materials are also covered. Any risks that may emanate from starting materials of inappropriate quality must be avoided for the benefit and safety of patients using medicinal products. In 1995 and 1996 more than 80 children died in Haïti following ingestion of a cough-and-cold syrup containing glycerol contaminated with diethylene glycol. During the last 60 years worldwide more than 500 patients have died due to such intoxications. This fact has induced WHO to convene a consultation on the production of starting materials¹ of good quality, the maintenance of that quality throughout the distribution chain, and the confirmation of the quality by the users of starting materials. The objective was to formulate recommendations for the parties concerned.

2. Evaluation of the general situation

2.1 Production of starting materials

The production of quality starting materials must be carefully planned in order to obtain starting materials which are both suitable and safe for the intended purpose. This includes the quality of raw materials for the production of starting materials, including purification steps, and quality control of the finished product – including in-process controls, batch release and, if appropriate, the stability of the product in its container. In other words, starting materials should be produced according to

¹ Starting materials covered by this report include any material used in manufacturing a pharmaceutical product or that would come into contact with the finished product. This includes materials such as: active pharmaceutical ingredients (APIs), excipients, packaging materials in direct contact with the product, propellants, and the like.

appropriate quality standards. For active substances this is generally accepted and already provided for by good manufacturing practices (GMP) guidelines published by WHO² or under development.³ All parties in the chain from the production of starting materials to the manufacture of the final product have responsibility for their actions, which must be documented in compliance with established GMP. However, the ultimate responsibility remains with the manufacturer of the final drug product. National or international regulations are currently being implemented or are in the process of being developed.

Excipients are rarely produced specifically for pharmaceutical purposes. The majority of the frequently used pharmaceutical excipients are mainly utilized in food or cosmetics, which may be, but probably are not, produced according to GMP. Certain excipients even have their main use in completely different fields like paint, building materials, refrigeration, etc. Some excipients are being specifically manufactured for pharmaceutical application, in which case full GMP for active substances should be applied. In this instance, the same principles should be applied as for the production of active substances, i.e. GMP.⁴ In any case, excipients should at least be produced under appropriate quality standards and a quality management system such as ISO 9000. Chemicals that are principally used for purposes other than pharmaceutical or nutritional supplements may also be used as active substances or excipients for the production of medicinal products. In this case, it cannot be expected that these substances are produced according to GMP because the manufacturer may not be aware of the pharmaceutical use of the substance, for instance, as the amount used pharmaceutically can be very small. Such a substance becomes a pharmaceutical starting material when it is specifically designated as such, e.g. by labelling it as complying with a pharmacopoeial monograph, such as those published in Ph. Eur. or USP. From this point on, all following steps should be performed under GMP. Although it is generally accepted that quality must be built in to a product during its production, this rule cannot be applied here. Therefore, the designation as a pharmaceutical starting material of such substances deserves special consideration and must be well founded and documented. The status of each manufacturing process should be clear and the test methods necessary for quality control should be defined as a function of the quality system in place.

Containers, including closures, may or may not be regarded as belonging to the category of starting materials. However, since they come into close contact with the dosage form and the starting materials and are often intended to protect them from deterioration – such as that caused by light – they may have an important influence on the stability of the medicinal product.

Consequently they must be of suitable and consistent quality and should also be produced employing a suitable quality management system, such as GMP or the ISO

² *Good Manufacturing Practices for Pharmaceutical Products (GMP)*, WHO Technical Report Series, No. 823, 1992, Annex 1, pp. 77-79.

³ *Internationally Harmonised Guide for Active Pharmaceutical Ingredients, Good Manufacturing Practice (API Guide)*. Draft, September 1997, Pharmaceutical Inspection Convention and Co-operation Scheme (PIC-PIC/S).

⁴ *Good Manufacturing Practices: supplementary guidelines for the manufacture of pharmaceutical excipients*, WHO Technical Report Series, No. 885, Annex 5, 1998 (in print).

9000 series. A certificate of analysis and good record keeping of documentation will also be required for packaging materials intended for pharmaceutical use.

2.2 *Distribution and trade*

Labelling and packaging⁵ are a usual practice of a number of trading companies (brokers and wholesalers) for several reasons. This practice may be accompanied by changing certificates of analysis issued by the producers of the starting materials into certificates bearing only the name of the trading company. In addition, containers are sometimes used whose suitability to maintain the quality of the starting material has not been demonstrated. Labelling and/or packaging is usually performed by a forwarding company on behalf of the trading company and may not be under direct control of the trading company. Finally, storage and shipment are sometimes being performed under unsuitable conditions. Obviously improper trading practices can be an important risk to the quality of starting materials and consequently measures should be taken to prevent this risk by establishing good trading practices. In order to maintain the original quality, packaging, labelling (and re-)certification of any starting material must be carried out according to GMP, and storage, shipment and trade performed according to internationally accepted good distribution practices (GDP).

2.3 *Certification and its reliability*

Certificates of analysis that are not based on scientific results will be useless and may even be misleading as they may give the unjustified impression that a particular batch of a starting material is of suitable quality, when it is not. To prevent such a dangerous misinterpretation the supplier of a starting material should be qualified and authorized before accepting the certificates of analysis. Authorization of the supplier should be based on auditing in order to confirm his adherence to GMP or another suitable quality management system, such as the ISO 9000 series. This should include all subcontractors, repackagers and distributors and be periodically repeated. Authorization should be supplemented by testing an adequate number of lots and comparing the results obtained with those provided by the supplier, taking into consideration the suitability of test methods, in order to establish their equivalence. Furthermore the supplier must agree to inform the customer about all relevant changes in production.

Proper identification of starting materials is indispensable under all circumstances, even when the starting material is accompanied by a reliable certificate of analysis. The only alternative to the use of reliable and meaningful certificates is full testing of the quality of the starting material by its user according to suitable specifications and using suitable test methods. However, it must be kept in mind that quality must be built into a starting material during production. Consequently in any case it is important that the supplier and any certifier of a starting material employs a suitable quality management system.

Typical deficiencies in certificates of analysis are: lack of signature, copies instead of original certificates, incomplete test results rather than full results of all tests included

⁵ Labelling and packaging also include relabelling and repackaging in this document, i.e. the following text.

in the respective pharmacopoeial monographs, tests using less precise or less specific methods, different from those indicated in the relevant pharmacopoeia or product specification, lack of identification of the manufacturer of the material, and of the issue of the certificates, etc.

2.4 Nomenclature and standards

In contrast to active substances, no generally accepted nomenclature is available for the majority of excipients. To avoid mislabelling and misunderstanding in trade such an internationally accepted nomenclature system would be very useful. Another obstacle to the use of excipients by manufacturers of dosage forms, and to trade, is the fact that pharmacopoeial norms are not usually harmonized, sometimes resulting in different requirements.

Recommendations

All parties involved

- Starting materials purported to be used as a pharmaceutical starting material must meet all of the quality criteria suitable for the intended pharmaceutical use.
- Starting materials designated to be of pharmacopoeial quality should meet the respective requirements before the material can be labelled and accepted for the intended pharmaceutical use.
- Starting materials should be manufactured, handled and distributed according to GMP from the moment they are designated for pharmaceutical purposes.

Governments

- National and regional legislation on medicinal products should be extended to cover starting materials.
- National and regional legislation on medicinal products, including starting materials, should be extended to free ports.
- Key parties in the chain – producers, traders, forwarders, tenderers, brokers – must be authorized for their activities by the competent health authority of the country in which each activity occurs. Authorization should be appropriate for each key activity in the chain, in accordance with the risk assessment of the activities. Such authorization requires adequate inspection. Failure to follow the requirements of the authorization must have appropriate legal consequences. There should be free and open exchange of information on such cases between governments.
- GMP/GDP observance should be monitored by GMP/GDP inspection.

- Countries should be encouraged to only use starting materials that can be properly analysed within their setting.
- National and regional drug regulatory procedures should be extended to include excipients. These should be in the drug master files.

Manufacturers

- All pharmaceutical manufacturers must have access to suitably equipped analytical testing laboratories in order to control incoming materials and final products.

Traders and brokers

- Traders in starting materials should form an international association, which may serve as a partner in discussions on quality assurance of the trade of starting materials.
- All tendering of starting materials for pharmaceutical manufacture should include a condition that the material was manufactured in accordance with a suitable quality assurance system, such as GMP, and was handled appropriately throughout the entire distribution chain.

WHO

- WHO should issue guidance about the certificate of analysis, which should represent the original data, including the name of the manufacturer, the batch number, the results of qualitative and quantitative measurements, the methods used (specifications), and the signature of the issuer of the certificate of analysis.
- Where WHO programmes support or encourage local manufacture, GMP should be a first priority.
- WHO should develop an international nomenclature system for excipients.
- WHO should develop a model for risk assessment of excipients.
- WHO should identify excipients which are specifically considered to be of risk.
- WHO should develop an education programme covering active ingredients and excipients for all levels of handling of pharmaceutical materials (including starting materials manufacturers, traders, forwarders, distributors, finished product manufacturers and regulators).
- WHO should continue the development of simple alternative test methods for inclusion in *The International Pharmacopoeia*.

- WHO should develop a certification scheme for starting materials and encourage governments to use this mechanism.
- WHO should recommend that every country has access to an experienced laboratory that is suitably equipped.
- WHO should develop a guidance document for purchase of starting materials.
- WHO should develop a guidance document on Good Distribution Practices (GDP).
- WHO should develop an international database for starting materials for medicinal products.
