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Impact of Biosafety on GMP

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Most products of biotechnology are destined for distribution at home and abroad. A guide of the European Community to good manufacturing practice (GMP) for pharmaceutical products has therefore been established to facilitate the removal of barriers to trade in pharmaceuticals, to promote uniformity in licensing decisions, to ensure the maintaining of high standards of quality assurance in the development, manufacture and control of pharmaceutical products and for the mutual recognition of inspections. The holder of a manufacturing authorization must comprehensively design and carefully implement a system of quality assurance incorporating good manufacturing practice and thus quality control. The good manufacturing practice (GMP) includes also the standards for the establishment of the validity of test data (GLP) and the precaution measures to ensure the safety of man and the environment in respect to biological materials (biosafety).

The GMP guidelines lay down basic rules for the standardization of the production of pharmaceuticals and the control of their quality in conformity with the priciples of GLP. The GLP guidelines define the criteria to be applied in establishing the validity of test data and cover all aspects of the planning, conduct, control, documentation and reporting of laboratory experiments. The biosafety guidelines describe the standards necessary to ensure the safety of man and the environment including the relevant aspects of the assessment of the hazards of biological materials, the corresponding precaution measures and the establishment of these precautions. The biosafety standards are also implicit in the priciples of GMP, *e.g.* in the training of personnel and the personal hygiene. The GMP, GLP and biosafety guidelines are thus not separate codes of practice applicable in different fields, but they are interrelated and complement one another. The standards of biosafety are outlined below.

Hazards and the appropriate precautionary measures are respectively classified according to four risk categories and safety levels. These classifications are almost identical in the national (Switzerland) and international guidelines.

The naturally occurring organisms, of which no danger to man and the environment is known or has to be expected, are classified to Risk Category 1 [1][2]. Those included in Risk Categories 2, 3, and 4 [1] [2] can cause infections, or toxic effects, or can be detrimental to the environment. Genetically modified organisms are also assigned to Risk Categories 1–4 according to the potential dangers inherent in the DNA from the donor organism, the vectors and the recipient organisms. Although, by classification, the microorganisms included in Risk Category 1 present no direct danger, the occurrence of allergies, symptoms due to the release of endotoxins, or illness either following the ingestion of large quantities of such organisms or in compromised hosts cannot be excluded. The guidelines on safety measures to be adopted at Biosafety Level 1 therefore require that the risks of exposure of personnel to such organisms and their escape into the environment should be kept at the lowest practicable level by strict observance of the basic rules of hygiene and the adoption of approved microbiological practices. Where microorganisms belonging to Risk Category 1 are processed on a large scale (>100 l), the same measures for Biosafety Level 1 are recommended in the OECD guidelines for Good Industrial Large-Scale Practice (GILSP).

Biosafety Level 2 need only be touched upon in this context, because microorganisms assigned to Risk Category 2 are only rarely used in biotechnological processes. At this level, all possible precautions should be taken as a matter of routine to minimize any exposure of personnel and release of microorganisms into the environment as low as possible. This means no exposure and no release under normal conditions of the processes. It must be borne in mind that the potential hazards associated with micoorganisms of Risk Category 2 can be heterogenous, and must therefore be analysed individally before appropriate safety measures can be adopted. Strains of *Bifidobacterium dentium*, *e.g.*, require much less stringent measures than polioviruses or rabies virus. Biosafety Level 3 and 4 require much more elaborate precautionary measures relating to the design and structure of laboratories and production premises, installations and equipment.

The GMP and GLP guidelines are recommendations issued by the drug regulatory authorities and have no legal force. The biosafety standards, on the other hand, have been enacted by the legislature in Switzerland and most other countries. In Swiss law, the Ordinance on Protection against Major Accidents promulgated under the Environmental Protection Act [1] lays down regulations binding on all companies processing gentically modified microorganisms on a large scale and applying to all processes on a large scale involving naturally occurring microorganisms of Risk Categories 2–4. Companies are further obliged to notify the project leaders or to register such projects formally with the Swiss Commission on Biological Safety [2], if genetically modified microorganisms are involved. Although the Commission has no legal basis, its directives have to be obeyed, since the legislature may insist these guidelines must be folowed in conformity with the state of the art.

In the light of the above regulations and recommendations, it can be concluded that the biosafety standards must always be compiled with wherever genetically modified microorganisms and certain naturally occurring organisms are processed on a large scale, and that these standards are embodied in the GMP requirements. The other GMP requirements are only mandatory if products have to be approved by the registration authorities.

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[1] Störfallverordnung (Ordinance on Protection against Major Accidents), Handbuch II, Richtlinien für Betriebe mit Mikroorganismen, Eidgenössische Drucksachen und Materialzentrale, Form 319. 761d 2.92.

[2] Guidelines of the Interdisciplinary Swiss Commission for Biological Safety in Research and Technology. Secretariat. Apfelbaumstrasse 43, CH–8050 Zürich.