

EU Guide to  
**Good  
Manufacturing  
Practice**

for Medicinal Products  
for Human and Veterinary Use  
8th edition 2016

Revised:  
Part II  
Annexes 15, 16

Compiled and edited by  
Gert Auterhoff and Siegfried Throm



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# EU Guide to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

8th revised and enlarged edition 2016

Compiled and edited by Gert Auterhoff  
and Siegfried Throm



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## Editors' Introduction

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (**EC GMP Directive**) (O. J. No L 262 of 14 October 2003, pp. 22) adapts the provisions of Directive 91/365/EEC (**previous GMP Directive**) (O. J. No L 193 of 17 July 1991, pp. 30) and extends them to include investigational medicinal products. Thus Directive 2003/94/EC replaces Directive 91/365/EEC. It is based on Article 47 of Directive 2001/83/EC (O. J. No L 311 of 28 November 2001, pp. 67), according to which the principles and guidelines of good manufacturing practices shall be adopted in the form of a directive. The Directive 2003/94/EC was adopted also in consideration of Article 13 (3) of Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001 (O. J. No L 121 of May 1, 2001, pp. 34).

Directive 2003/94/EC became effective on 3 November 2003 and called upon the Member States to bring into force the new legislation by 30 April 2004 at the latest. In Germany this directive was transposed into national law with the “Third Ordinance amending the Pharmaceutical Operation Ordinance” (Dritte Verordnung zur Änderung der Betriebsverordnung für pharmazeutische Unternehmer – PharmBetrV) of 10 August 2004 (Federal Law Gazette – BGBl. I, pp. 2155). Moreover, the Commission published comprehensive guidelines in line with the above principles.

In January 1989, the EEC Commission published an English edition of the above guidelines as document III/2244/87-EN, Rev. 3 “EEC Guide to Good Manufacturing Practice for Medicinal Products” as final version. The German translation, which had been agreed upon with the competent authorities of Austria and Switzerland, was completed in May 1990. The Commission agencies had decided to publish the guideline in its current form in order to advise both the pharmaceutical industry and the national monitoring authorities of what the authorities responsible for establishing the regulations currently consider as “compliance with the Good Manufacturing Practice”.

Meanwhile, the original directive introducing the principles as mandatory has been changed to Commission Directive 2003/94/EC, which is published below (pp. 11) followed by the Commission Directive of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products (91/412/EEC) (pp. 20). The “EEC Guide to Good Manufacturing Practice for Medicinal Products” (III/2244/87, Rev. 3 January 1989), which entered into force on 1 January 1992, is published on pp. 27.

The EEC Commission had published the following 14 Annexes for certain groups of medicinal products, test methods, manufacturing processes and circumstances:

1. Manufacture of sterile medicinal products
2. Manufacture of biological medicinal products for human use
3. Manufacture of radiopharmaceuticals
4. Manufacture of veterinary medicinal products other than immunologicals
5. Manufacture of immunological veterinary medicinal products

6. Manufacture of medicinal gases
7. Manufacture of herbal medicinal products
8. Sampling of starting and packaging materials
9. Manufacture of liquids, creams and ointments
10. Manufacture of pressurised metered dose aerosol preparations for inhalation
11. Computerised systems
12. Use of ionising radiation in the manufacture of medicinal products
13. Manufacture of investigational medicinal products
14. Manufacture of products derived from human blood or human plasma.

Whereas the annexes for the manufacture of sterile medicinal products and the EC GMP Guide had come into operation on 1 January 1992, annexes No 2–14 were to be applied as from 1 January 1993 respectively 1 July 1993. Both the GMP guide and most of the annexes have been revised repeatedly and there was a major re-structuring of the GMP guide, leading to Part I for medicinal products for human and veterinary use and Part II for active substances used as starting materials, implementing Directives 2004/27/EC and 2004/28/EC.

In the course of the year 2001, the following four annexes were added:

15. Qualification and Validation (July 2001)
16. Certification by a Qualified Person and Batch Release (July 2001)
17. Parametric Release (July 2001)
18. Good manufacturing practice for active pharmaceutical ingredients (API) (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-ICH)

Annex 18 is identical with the ICH Guideline Q7A from November 2000 and resulted from a new legislative provision requiring pharmaceutical manufacturers to use only active substances which have been manufactured according to GMP in the manufacture of medicinal products and came into operation in July 2001.

After a re-structuring process of the GMP Guide this annex was published as GMP Part II (October 2005).

The deadline for application by Member States of the new legislation for active substances used as starting materials in the manufacture of human and veterinary medicinal products was 30 October 2005.

In December 2005, another annex was published, coming into operation on 1 June 2006: Annex 19 “Reference and Retention Samples”, followed by Annex 20 “Quality Risk Management” in February 2008.

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## Extended Editors' Introduction

Compared to the 7th edition published in 2012 the following revisions have been made in the 8th edition 2016:

- Revision of Chapter 2 Personnel (16 February 2014)
- Revision of Chapter 3 Premises and Equipment (1 March 2015)
- Revision of Chapter 5 Production (1 March 2015)
- Revision of Chapter 6 Quality Control (1 October 2014)
- Revision of Chapter 8 Complaints and Product Recall (1 March 2015)
- Revision of Part II (1 September 2014)
- Revision of Annex 15 (1 October 2015)
- Revision of Annex 16 (15 April 2016)

All dates are application dates rather than publication dates.

Furthermore the 8th edition has been extended by The Commission Delegated Regulation (EU) No. 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use (application date: from 25 May 2015).

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# Guide to Good Manufacturing Practice (GMP) for Medicinal Products for Human and Veterinary Use

## Introduction of the European Commission (December 2010)

The pharmaceutical industry of the European Union maintains high standards of Quality Management in the development, manufacture and control of medicinal products. A system of marketing authorisations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of manufacturing authorisations ensures that all products authorised on the European market are manufactured/imported only by authorised manufacturers, whose activities are regularly inspected by the competent authorities, using Quality Risk Management principles. Manufacturing authorisations are required by all pharmaceutical manufacturers in the European Union whether the products are sold within or outside of the Union.

Two directives laying down principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products were adopted by the Commission. Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use. Detailed guidelines in accordance with those principles are published in the Guide to Good Manufacturing Practice which will be used in assessing applications for manufacturing authorisations and as a basis for inspection of manufacturers of medicinal products.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations referred to in Article 40 of Directive 2001/83/EC, in Article 44 of Directive 2001/82/EC and Article 13 of Directive 2001/20/EC, as amended respectively. They are also relevant for pharmaceutical manufacturing processes, such as those undertaken in hospitals.

All Member States and the industry agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use. Certain detailed adjustments to the GMP guidelines are set out in two annexes specific to veterinary medicinal products and to immunological veterinary medicinal products.

The Guide is presented in three parts and supplemented by a series of annexes. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials. Part III contains GMP related documents, which clarify regulatory expectations.

Chapters of Part I on “basic requirements” are headed by principles as defined in Directives 2003/94/EC and 91/412/EEC. Chapter 1 on Quality Management outlines the fundamental concept of quality management as applied to the manufacture of medicinal products. Thereafter, each chapter has a principle outlining the quality management objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle.

According to the revised Article 47 and Article 51, respectively, of the Directive 2001/83/EC and Directive 2001/82/EC, as amended, detailed guidelines on

the principles of GMP for active substances used as starting materials shall be adopted and published by the Commission. Part II was established on the basis of a guideline developed on the level of ICH and published as ICH Q7A on “active pharmaceutical ingredients”. It has an extended application both for the human and the veterinary sector.

In addition to the general matters of Good Manufacturing Practice outlined in Part I and II, a series of annexes providing detail about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously (e.g. annex on sterile preparations and on radiopharmaceuticals and/or on biological medicinal products).

A glossary of some terms used in the Guide has been incorporated after the annexes. Part III is intended to host a collection of GMP related documents, which are not detailed guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC. The aim of Part III is to clarify regulatory expectations and it should be viewed as a source of information on current best practices. Details on the applicability will be described separately in each document.

The Guide is not intended to cover safety aspects for the personnel engaged in manufacture. This may be particularly important in the manufacture of certain medicinal products such as highly active, biological and radioactive medicinal products. However, those aspects are governed by other provisions of Union or national law.

Throughout the Guide, it is assumed that the requirements of the Marketing Authorisation relating to the safety, quality and efficacy of the products, are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorisation.

For many years, the manufacture of medicinal products has taken place in accordance with guidelines for Good Manufacturing Practice and the manufacture of medicinal products is not governed by CEN/ISO standards. The CEN/ISO standards have been considered but the terminology of these standards has not been implemented in this edition. It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Management. The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Management at least equivalent to those set out in this Guide.

The GMP guide will be regularly revised in order to reflect continual improvement of best practices in the field of Quality. Revisions will be made publicly available on the website of the European Commission:

[http://ec.europa.eu/health/documents/eudralex/vol-4/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm)

COMMISSION DIRECTIVE 2003/94/EC  
of 8 October 2003

**Laying down the principles and guidelines of good manufacturing  
practice in respect of medicinal products for human use and  
investigational medicinal products for human use**

(Text with EEA relevance)

Nur für den privaten oder firmeninternen Gebrauch / For private or internal corporate use only

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,  
Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use<sup>1)</sup>, as last amended by Commission Directive 2003/63/EC<sup>2)</sup>, and in particular Article 47 thereof,

Whereas:

- (1) All medicinal products for human use manufactured or imported into the Community, including medicinal products intended for export, are to be manufactured in accordance with the principles and guidelines of good manufacturing practice.
- (2) Those principles and guidelines are set out in Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use<sup>3)</sup>.
- (3) Article 13(3) of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use<sup>4)</sup> requires that detailed guidance be drawn up, in accordance with the guidelines on good manufacturing practice, on the elements to be taken into account when evaluating investigational medicinal products for human use with the object of releasing batches within the Community.
- (4) It is therefore necessary to extend and adapt the provisions of Directive 91/356/EEC to cover good manufacturing practice of investigational medicinal products.
- (5) Since most of the provisions of Directive 91/356/EEC need to be adjusted, for the sake of clarity that Directive should be replaced.

<sup>1)</sup> OJ L 311, 28. 11. 2001, p. 67.

<sup>2)</sup> OJ L 159, 27. 6. 2003, p. 46.

<sup>3)</sup> OJ L 193, 17. 7. 1991, p. 30.

<sup>4)</sup> OJ L 121, 1. 5. 2001, p. 34.

- (6) In order to ensure conformity with the principles and guidelines of good manufacturing practice, it is necessary to lay down detailed provisions on inspections by the competent authorities and on certain obligations of the manufacturer.
- (7) All manufacturers should operate an effective quality management system of their manufacturing operations, which requires the implementation of a pharmaceutical quality assurance system.
- (8) Principles and guidelines of good manufacturing practice should be set out in relation to quality management, personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self-inspection.
- (9) In order to protect the human beings involved in clinical trials and to ensure that investigational medicinal products can be traced, specific provisions on the labelling of those products are necessary.
- (10) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use, set up under Article 121 of Directive 2001/83/EC,

HAS ADOPTED THIS DIRECTIVE:

#### Article 1

##### Scope

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 40 of Directive 2001/83/EC and in respect of investigational medicinal products for human use whose manufacture requires the authorisation referred to in Article 13 of Directive 2001/20/EC.

#### Article 2

##### Definitions

For the purposes of this Directive, the following definitions shall apply:

1. 'medicinal product' means any product as defined in Article 1(2) of Directive 2001/83/EC;
2. 'investigational medicinal product' means any product as defined in Article 2(d) of Directive 2001/20/EC;
3. 'manufacturer' means any person engaged in activities for which the authorisation referred to in Article 40(1) and (3) of Directive 2001/83/EC or the authorisation referred to in Article 13(1) of Directive 2001/20/EC is required;
4. 'qualified person' means the person referred to in Article 48 of Directive 2001/83/EC or in Article 13(2) of Directive 2001/20/EC;
5. 'pharmaceutical quality assurance' means the total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use;

6. 'good manufacturing practice' means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use;
7. 'blinding' means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;
8. 'unblinding' means the disclosure of the identity of a blinded product.

### Article 3

#### Inspections

1. By means of the repeated inspections referred to in Article 111(1) of Directive 2001/83/EC and by means of the inspections referred to in Article 15(1) of Directive 2001/20/EC, the Member States shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by this Directive. Member States shall also take into account the compilation, published by the Commission, of Community procedures on inspections and exchange of information.
2. For the interpretation of the principles and guidelines of good manufacturing practice, the manufacturers and the competent authorities shall take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in the 'Guide to good manufacturing practice for medicinal products and for investigational medicinal products'.

### Article 4

#### Conformity with good manufacturing practice

1. The manufacturer shall ensure that manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorisation. This provision shall also apply to medicinal products intended only for export.
2. For medicinal products and investigational medicinal products imported from third countries, the importer shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down by the Community.

In addition, an importer of medicinal products shall ensure that such products have been manufactured by manufacturers duly authorised to do so. An importer of investigational medicinal products shall ensure that such products have been manufactured by a manufacturer notified to the competent authorities and accepted by them for that purpose.

### Article 5

#### Compliance with marketing authorisation

1. The manufacturer shall ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as accepted by the competent authorities. In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information provided by the sponsor pursuant to Article 9(2) of Directive 2001/20/EC as accepted by the competent authorities.

2. The manufacturer shall regularly review his manufacturing methods in the light of scientific and technical progress and the development of the investigational medicinal product.  
If a variation to the marketing authorisation dossier or an amendment to the request referred to in Article 9(2) of Directive 2001/20/EC is necessary, the application for modification shall be submitted to the competent authorities.

#### Article 6

##### Quality assurance system

The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different departments.

#### Article 7

##### Personnel

1. At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the pharmaceutical quality assurance objective.
2. The duties of the managerial and supervisory staff, including the qualified persons, responsible for implementing and operating good manufacturing practice, shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.
3. The staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibility correctly.
4. The personnel shall receive initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance and good manufacturing practice, and, where appropriate, the particular requirements for the manufacture of investigational medicinal products.
5. Hygiene programmes adapted to the activities to be carried out shall be established and observed. These programmes shall, in particular, include procedures relating to health, hygiene practice and clothing of personnel.

#### Article 8

##### Premises and equipment

1. Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended operations.
2. Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.
3. Premises and equipment to be used for manufacturing operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation.

## Article 9 Documentation

1. The manufacturer shall establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed. Documents shall be clear, free from error and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product to be traced.

For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

For an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation.

2. When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained.

## Article 10 Production

1. The different production operations shall be carried out in accordance with pre-established instructions and procedures and in accordance with good manufacturing practice. Adequate and sufficient resources shall be made available for the inprocess controls. All process deviations and product defects shall be documented and thoroughly investigated.
2. Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups. In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.
3. For medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated.



4. For investigational medicinal products, the manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development. At least the critical process steps, such as sterilisation, shall be validated. All steps in the design and development of the manufacturing process shall be fully documented.

## Article 11

### Quality control

1. The manufacturer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.  
That person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of the starting materials and packaging materials and the testing of intermediate and finished products.
2. For medicinal products, including those imported from third countries, contract laboratories may be used if authorised in accordance with Article 12 of this Directive and point (b) of Article 20 of Directive 2001/83/EC. For investigational medicinal products, the sponsor shall ensure that the contract laboratory complies with the content of the request referred to in Article 9(2) of Directive 2001/20/EC, as accepted by the competent authority. When the products are imported from third countries, analytical control shall not be mandatory.
3. During the final control of the finished product before its release for sale or distribution or for use in clinical trials, the quality control system shall take into account, in addition to analytical results, essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications, including the final finished pack.
4. Samples of each batch of finished medicinal product shall be retained for at least one year after the expiry date.  
For an investigational medicinal product, sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished product batch shall be retained for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.  
Unless a longer period is required under the law of the Member State of manufacture, samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. All those samples shall be maintained at the disposal of the competent authorities.  
Other conditions may be defined, by agreement with the competent authority, for the sampling and retaining of starting materials and certain products manufactured individually or in small quantities, or when their storage could raise special problems.

Article 12  
Work contracted out

1. Any manufacturing operation or operation linked thereto which is carried out under contract shall be the subject of a written contract.
2. The contract shall clearly define the responsibilities of each party and shall define, in particular, the observance of good manufacturing practice to be followed by the contract-acceptor and the manner in which the qualified person responsible for certifying each batch is to discharge his responsibilities.
3. The contract-acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract-giver.
4. The contract-acceptor shall comply with the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities pursuant to Article 111 of Directive 2001/83/ EC and Article 15 of Directive 2001/20/EC.

Article 13  
Complaints, product recall and emergency unblinding

1. In the case of medicinal products, the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination.  
Any recall shall be made in accordance with the requirements referred to in Article 123 of Directive 2001/83/EC.
2. In the case of investigational medicinal products, the manufacturer shall, in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products which have already entered the distribution network. The manufacturer shall record and investigate any complaint concerning a defect and shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply.  
In the case of investigational medicinal products, all trial sites shall be identified and, in so far as is possible, the countries of destination shall be indicated.  
In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised medicinal product.

3. The sponsor shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall as referred to in paragraph 2. The sponsor shall ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

#### Article 14 Self-inspection

The manufacturer shall conduct repeated self-inspections as part of the quality assurance system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures. Records shall be maintained of such self-inspections and any corrective action subsequently taken.

#### Article 15 Labelling

In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.

#### Article 16 Repeal of Directive 91/356/EEC

Directive 91/356/EEC is repealed.

References to the repealed Directive shall be construed as references to this Directive.

#### Article 17 Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 30 April 2004 at the latest. They shall forthwith communicate to the Commission the text of the provisions and correlation table between those provisions and the provisions of this Directive.  
When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. The Member States shall determine how such reference is to be made.
2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

#### Article 18 Entry into force

This Directive shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

Article 19  
Addressees

This Directive is addressed to the Member States.

Done at Brussels, 8 October 2003.

*For the Commission*

**Erkki LIIKANEN**  
*Member of the Commission*

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**COMMISSION DIRECTIVE 91/412/EEC**  
of 23 July 1991

**laying down the principles and guidelines of good manufacturing  
practice for veterinary medicinal products**

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,  
Having regard to Council Directive 81/851/EEC of 28 September 1981 concerning the approximation of the laws of the Member States relating to veterinary medicinal products<sup>1)</sup>, as last amended by Directive 90/676/EEC<sup>2)</sup>, and in particular Article 27a,

Having regard to Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products<sup>3)</sup>,  
Whereas all veterinary medicinal products manufactured or imported into the Community, including medicinal products intended for export should be manufactured in accordance with the principles and guidelines of good manufacturing practice;

Whereas, in accordance with national legislation, Member States may require compliance with these principles of good manufacturing practice during the manufacture of products intended for use in clinical trials;

Whereas the detailed guidelines mentioned in Article 27a of Directive 81/851/EEC have been published by the Commission after consultation with the pharmaceutical inspection services of the Member States in the form of a 'Guide to good manufacturing practice for medicinal products';

Whereas it is necessary that all manufacturers should operate an effective quality management of their manufacturing operations, and that this requires the implementation of a pharmaceutical quality assurance system;

Whereas officials representing competent authorities should report on whether the manufacturer complies with good manufacturing practice and that these reports should be communicated upon reasoned request to the competent authorities of another Member State;

Whereas the principles and guidelines of good manufacturing practice should primarily concern personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self inspection;

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<sup>1)</sup> OJ No L 317, 6. 11. 1981, p. 1.

<sup>2)</sup> OJ No L 373, 31. 12. 1990, p. 15.

<sup>3)</sup> OJ No L 373, 31. 12. 1990, p. 26.