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

Seventh revised edition

Compiled and edited by Gert Auterhoff and Siegfried Throm

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# Content

Editors' Introduction ........................................................................................................... 8

Extended Editors’ Introduction .......................................................................................... 10


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

Introduction of the European Commission ........................................................................ 27

**Part I – Basic Requirements for Medicinal Products** .................................................. 29

Chapter 1: Pharmaceutical Quality System (Revised June 2012) ................................. 29

Chapter 2: Personnel ......................................................................................................... 35

Chapter 3: Premises and Equipment .................................................................................. 39

Chapter 4: Documentation (Revised January 2011) ....................................................... 43

Chapter 5: Production ......................................................................................................... 51

Chapter 6: Quality Control (Revised October 2005) .................................................... 57

Chapter 7: Outsourced Activities (Revised June 2012) ................................................ 62

Chapter 8: Complaints and Product Recall (Revised December 2005) ...................... 65

Chapter 9: Self-Inspection ................................................................................................. 67
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part II – Basic Requirements for Active Substances used as Starting</td>
<td>69</td>
</tr>
<tr>
<td>Materials</td>
<td></td>
</tr>
<tr>
<td>1 Introduction</td>
<td>71</td>
</tr>
<tr>
<td>2 Quality Management</td>
<td>74</td>
</tr>
<tr>
<td>3 Personnel</td>
<td>76</td>
</tr>
<tr>
<td>4 Buildings and Facilities</td>
<td>77</td>
</tr>
<tr>
<td>5 Process Equipment</td>
<td>80</td>
</tr>
<tr>
<td>6 Documentation and Records</td>
<td>82</td>
</tr>
<tr>
<td>7 Materials Management</td>
<td>86</td>
</tr>
<tr>
<td>8 Production and In-Process Controls</td>
<td>88</td>
</tr>
<tr>
<td>9 Packaging and Identification Labelling of APIs and Intermediates</td>
<td>91</td>
</tr>
<tr>
<td>10 Storage and Distribution</td>
<td>92</td>
</tr>
<tr>
<td>11 Laboratory Controls</td>
<td>93</td>
</tr>
<tr>
<td>12 Validation</td>
<td>96</td>
</tr>
<tr>
<td>13 Change Control</td>
<td>100</td>
</tr>
<tr>
<td>14 Rejection and Re-Use of Materials</td>
<td>101</td>
</tr>
<tr>
<td>15 Complaints and Recalls</td>
<td>102</td>
</tr>
<tr>
<td>16 Contract Manufacturers (Including Laboratories)</td>
<td>103</td>
</tr>
<tr>
<td>17 Agents, Brokers, Traders, Distributors, Repackers and Relabellers</td>
<td>103</td>
</tr>
<tr>
<td>18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation</td>
<td>105</td>
</tr>
<tr>
<td>19 APIs for Use in Clinical Trials</td>
<td>108</td>
</tr>
<tr>
<td>20 Glossary</td>
<td>110</td>
</tr>
<tr>
<td>Part III – GMP Related Documents</td>
<td>117</td>
</tr>
<tr>
<td>Site Master File</td>
<td>118</td>
</tr>
<tr>
<td>Quality Risk Management (ICH Q9)</td>
<td>124</td>
</tr>
<tr>
<td>Note for Guidance on Pharmaceutical Quality System (ICH Q10)</td>
<td>142</td>
</tr>
<tr>
<td>MRA Batch Certificate (Revised May 2011)</td>
<td>159</td>
</tr>
<tr>
<td>Template for the ‘written confirmation’ for active substances exported</td>
<td>163</td>
</tr>
<tr>
<td>to the European Union for medicinal products for human use</td>
<td></td>
</tr>
</tbody>
</table>
Annexes

Annex 1. Manufacture of Sterile Medicinal Products
(Revised November 2008) ............................................................... 165

Annex 2. Manufacture of Biological active substances and
Medicinal Products for Human Use (Revised June 2012)........ 181

Annex 3. Manufacture of Radiopharmaceuticals
(Revised August 2008) .................................................................. 210

Annex 4. Manufacture of Veterinary Medicinal Products other
than Immunological Veterinary Medicinal Products ......... 217

Annex 5. Manufacture of Immunological Veterinary Medicinal
Products .......................................................................................... 219

Annex 6. Manufacture of Medicinal Gases (Revised January 2010).... 228

Annex 7. Manufacture of Herbal Medicinal Products
(Revised September 2008) .............................................................. 238

Annex 8. Sampling of Starting and Packaging Materials ............ 243

Annex 9. Manufacture of Liquids, Creams and Ointments ............ 245

Annex 10. Manufacture of Pressurised Metered Dose Aerosol
Preparations for Inhalation .............................................................. 246


Annex 12. Use of Ionising Radiation in the Manufacture
of Medicinal Products ..................................................................... 253

Annex 13. Manufacture of Investigational Medicinal Products
(Revised January 2010) .................................................................. 259

Annex 14. Manufacture of Medicinal Products derived from Human
Blood or Human Plasma (Revised May 2011)......................... 277

Annex 15. Qualification and Validation ............................................ 290

Annex 16. Certification by a Qualified Person and Batch Release
(July 2001) ...................................................................................... 297

Annex 17. Parametric Release ........................................................... 305

Annex 18. (Covered by Part II)

Annex 19. Reference and Retention Samples ............................... 308

Annex 20 (Covered by Part III/Q9)

Glossary .......................................................................................... 312
Editors' Introduction


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 immunologically
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.


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Extended Editors' Introduction

Since the publication of the 6th edition in 2009 the following changes have been made:
- Revision of the Introduction of the European Commission (December 2010)
- Revision including renaming of Chapter 1 Pharmaceutical Quality System (June 2012)
- Revision of Chapter 4 Documentation (January 2011)
- Revision including renaming of Chapter 7 Outsourced Activities (June 2012)
- Revision of Part II Basic Requirements for Active Substances
- Addition of Part III GMP Related Documents (December 2010) which hosts a collection of GMP related documents to clarify regulatory expectations
- Revision of Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use (June 2012)
- Revision of Annex 6 Manufacture of Medicinal Gases (January 2010)
- Revision of of Annex 11 Computerised Systems (January 2011)
- Revision of Annex 13 Manufacture of Investigational Medicinal Products (January 2010)
- Revision of Annex 14 Manufacture of Products derived from Human Blood or Human Plasma (May 2011)
- Transfer of Annex 20 Quality Risk Management from the Annexes to Part III

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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)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

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.


(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\(^4\) 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.

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\(^{1}\) OJ L 311, 28.11.2001, p. 67.
\(^{2}\) OJ L 159, 27.6.2003, p. 46.
\(^{4}\) OJ L 121, 1.5.2001, p. 34.
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.

All manufacturers should operate an effective quality management system of their manufacturing operations, which requires the implementation of a pharmaceutical quality assurance system.

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.

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.

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;


(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;
‘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;

‘blinding’ means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;

‘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.
Part III – GMP Related Documents

- Site Master File
- Quality Risk Management (ICH Q9)
- Note for Guidance on Pharmaceutical Quality System (ICH Q10)
- Internationally Harmonised Requirements for Batch Certification
- Template for the ‘written confirmation’ for active substances exported to the European Union for medicinal products for human use
These notes are intended to provide guidance on the recommended content of the Site Master File. A requirement for a Site Master File is referred to in Chapter 4 of the GMP Guide.

1. Introduction

1.1 The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

1.2 When submitted to a regulatory authority, the Site Master File should provide clear information on the manufacturer’s GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

1.3 A Site Master File should contain adequate information but, as far as possible, not exceed 25-30 pages plus appendices. Simple plans outline drawings or schematic layouts are preferred instead of narratives. The Site Master File, including appendices, should be readable when printed on A4 paper sheets.

1.4 The Site Master File should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The Site Master File should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each Appendix can have an individual effective date, allowing for independent updating.

2. Purpose

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that is useful to the regulatory authority in planning and conducting GMP inspections.

3. Scope

These Explanatory Notes apply to the preparation and content of the Site Master File. Manufacturers should refer to regional/national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File. These Explanatory Notes apply for all kind of manufacturing operations such as production, packaging and labelling, testing, relabeling and repackaging of
all types of medicinal products. The outlines of this guide could also be used in the preparation of a Site Master File or corresponding document by Blood and Tissue Establishments and manufacturers of Active Pharmaceutical Ingredients.

4. Content of Site Master File
Refer to the Annex for the format to be used.

Annex: Content of Site Master File

1. General Information on the Manufacturer

1.1 Contact information on the manufacturer
- Name and official address of the manufacturer;
- Names and street addresses of the site, buildings and production units located on the site;
- Contact information of the manufacturer including 24 hrs telephone number of the contact personnel in the case of product defects or recalls.
- Identification number of the site as e.g. GPS details, or any other geographic location system, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the site1)

1.2 Authorised pharmaceutical manufacturing activities of the site.
- Copy of the valid manufacturing authorisation issued by the relevant Competent Authority in Appendix 1; or when applicable, reference to the EudraGMP database. If the Competent Authority does not issue-manufacturing authorizations, this should be stated.
- Brief description of manufacture, import, export, distribution and other activities as authorized by the relevant Competent Authorities including foreign authorities with authorized dosage forms/activities, respectively; where not covered by the manufacturing authorization;
- Type of products currently manufactured on-site (list in Appendix 2) where not covered by Appendix 1 or EudraGMP entry;
- List of GMP inspections of the site within the last 5 years; including dates and name/country of the Competent Authority having performed the inspection. A copy of current GMP certificate (Appendix 3) or reference to the EudraGMP database, should be included, if available.

1.3 Any other manufacturing activities carried out on the site
- Description of non-pharmaceutical activities on-site, if any.

1) A D-U-N-S reference is required for Site Master Files submitted to EU/EEA authorities for manufacturing sites located outside of the EU/EEA.