



European Medicines Agency

London, 20 June 2005
Doc. Ref. EMEA/P/24143/2004

PROCEDURE FOR EUROPEAN UNION GUIDELINES AND RELATED DOCUMENTS WITHIN THE PHARMACEUTICAL LEGISLATIVE FRAMEWORK

INTERNAL DISCUSSION	mid-2003 to May 2004
TRANSMISSION TO CXMP	May 2004
DISCUSSION IN RELEVANT WORKING PARTIES	May - June 2004
TRANSMISSION TO CXMP	July 2004
RELEASE FOR CONSULTATION	September 2004
DEADLINE FOR COMMENTS	8 th December 2004
TRANSMISSION TO CONCERNED COMMITTEES AND GROUPS FOR INFORMATION	May 2005
PROPOSED DATE FOR PUBLICATION	End June 2005
DATE FOR COMING INTO OPERATION	1 September 2005

Public

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int <http://www.emea.eu.int>

©EMEA 2005 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

EXECUTIVE SUMMARY

The purpose of this paper is to describe and define the different guidelines that support the European pharmaceutical legislative framework and to describe a harmonised procedure for their development. It is intended to propose a consistent and transparent approach to the assessment of the need for guidance and the impact for interested parties and competent authorities, as well as the development, consultation and publication of these guidelines and their preparatory documents, taking into account the EMEA Transparency policy, and the findings of the CPMP¹ audit that was conducted in 2003.

The paper describes the different types of guidelines that can be considered to form part of the European pharmaceutical legislative framework and explains how these fit into the annual work programmes of the EMEA.

It outlines a transparent procedure for the development, consultation, finalisation and implementation of guidelines and makes reference to other related non-guideline documents.

It updates and replaces previously published and draft guidance in this area, in particular the European Commission paper on *Procedure for European Union Guidelines*.

¹ Now known as the Committee for Medicinal Products for Human Use (CHMP)

PROCEDURE FOR EUROPEAN UNION GUIDELINES AND RELATED DOCUMENTS WITHIN THE PHARMACEUTICAL LEGISLATIVE FRAMEWORK

1. INTRODUCTION

The body of European Union legislation in the pharmaceutical sector is compiled in the publications “*The Rules governing medicinal products in the European Union*”, Volume 1 and Volume 5.

The basic legislation is supported by a series of guidelines that are also published in the following volumes of *the Rules governing medicinal products in the European Union*:

- Volume 2 and 6 (*Notice to Applicants* and regulatory guidelines)
- Volume 3 and 7 (scientific guidelines)
- Volume 4 (GMP guidelines)
- Volume 8 (Maximum Residue Limits)
- Volume 9 (Pharmacovigilance guidelines),

and by additional guidance documents applying specifically to clinical trials (expected to be published as Volume 10), orphan medicinal products and good distribution practices (GDP), which are available either directly on the European Commission (<http://pharmacos.eudra.org/F2/eudralex/index.htm>) or EMEA (www.emea.eu.int) websites.

The purpose of this paper is to provide a general description of these guidance documents, and to detail in a transparent manner the procedure for their development.

It does not address procedural guidance documents outside the above frameworks nor guidance documents published by Heads of Medicines Agencies (human and veterinary).

It should also be noted that the process for the development and agreement on the *Notice to Applicants (Volume 2 + 6)* does not form a part of this paper.

It updates and replaces previously published and draft guidance in this area, in particular the European Commission paper on *Procedure for European Union Guidelines*, doc III/5354/96 Rev 18.10.96.

2. DEFINITIONS, TERMINOLOGY AND LEGAL STATUS

2.1 What is a guideline in the pharmaceutical legislative framework?

A **guideline** is a Community document, which is either referred to in the legislative framework as intended to fulfil a legal obligation laid down in the Community pharmaceutical legislation or considered to provide advice to applicants or marketing authorisation holders, competent authorities and/or other interested parties on the best or most appropriate way to fulfil an obligation laid down in the community pharmaceutical legislation. In the case of scientific guidelines, these may relate to specific scientific issues reflecting a harmonised EU approach and based on the most up-to-date scientific knowledge.

2.2 What is the legal status of guidelines?

The guidelines referred to hereafter may have different purposes and legal bases/status.

Within the framework of the pharmaceutical legislation, guidelines do not have legal force and the definitive legal requirements are those outlined in the relevant Community legislative framework (Directives, Regulations, Decisions etc.) as well as appropriate national rules. However, guidelines are to be considered as a harmonised Community position, which if they are followed by relevant parties such as the applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate assessment, approval and control of medicinal products in the European Union. Nevertheless, alternative approaches may be taken, provided that these are appropriately justified.

An exception to this general rule is the “Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” which is published in the Official Journal by the European Commission and updated regularly. In accordance with Directives 2001/82/EC and 2001/83/EC, this Note for Guidance has to be explicitly complied with.

2.3 Are there different terms used for different types of guidelines?

Historically the terms “note for guidance” and “guideline” have been used interchangeably. In this paper it is proposed that the term “guideline” be used prospectively as the unique term for guidance documents within the framework of “*The Rules Governing Medicinal Products in the European Union*”. The term guideline is the term generally used in the reference legislation.

For documents finalised before the entry into force of this procedure, the terms “guideline” and “note for guidance” should be considered to be synonymous. The different types of guidelines are described in section 3.

Within the various guideline frameworks (the volumes referred to above) guidelines may have different objectives. Historically these different types of guidelines may also have had different names.

For example, the terms “Position Paper” or “Points to consider” have been used for documents that express the current view of the Scientific Committees² to provide advice on:

- a selected area of medicinal product development where limited experience is available and knowledge is fast evolving, requiring the need for easy updates and flexibility.
- interpretation of guidelines or of technical requirements in the legislation.
- further elaboration of specific issues addressed in guidelines, for incorporation into the guideline upon its next revision.

2.4 What terms will be used in the future?

Since in effect the documents referred to above, also provide some guidance, the unique term “guidelines” will be used and any distinction with respect to limited experience and/or need for ongoing revision will be clearly outlined within the scope of the respective guideline.

3. TYPES OF GUIDELINES WITHIN THE PHARMACEUTICAL LEGISLATIVE FRAMEWORK

A summary of the different types of pharmaceutical guidelines is given below:

3.1 Regulatory Guidelines

The European Commission publishes in its *Notice to Applicants*, volumes 2C (human) and 6C (veterinary), a list of regulatory guidelines (<http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c> and <http://pharmacos.eudra.org/F2/eudralex/vol-6/home.htm>) related to procedural and regulatory requirements such as renewal procedures, dossier requirements for Type IA/IB variation notifications, summary of product characteristics (SPC), package information and classification for the supply, readability of the label and package leaflet requirements.

It should be noted that the process for the development and agreement on the *Notice to Applicants (Volume 2 + 6)* does not form a part of this paper. However, some procedural and regulatory guidelines relating to Community marketing authorisations may also be published by the scientific committees.

The EMEA also publishes procedural and technical guidance and document templates (Quality Review of Documents (QRD)) on its website. See section 3.12.

² The Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), or their legislative predecessors as appropriate

3.2 Scientific Guidelines related to Quality, Safety and Efficacy

Scientific guidelines are referred to in the annexes to Directives 2001/82/EC and 2001/83/EC and listed in the annexes to the Notice to Applicants implementing the Common Technical Document (CTD). The analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products are given in Directive 2001/82/EC and Directive 2001/83/EC as amended. In assembling the dossier for an application for a marketing authorisation, applicants shall take into account the scientific guidelines (including core summary of product characteristics, where applicable) relating to the quality, safety and efficacy of medicinal products as adopted by the scientific committees - the Committee for Medicinal Products for Human Use (CHMP)³ and the Committee for Medicinal Products for Veterinary Use (CVMP)⁴, the Committee on Herbal Medicinal Products (HMPC), and published by the European Medicines Agency (EMA).

These scientific guidelines aim to provide a basis for practical harmonisation of the manner in which Member States and EMA interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy. They are intended to give guidance to applicants and/or sponsors in planning the overall pharmaceutical product development, as well as the non-clinical and clinical tests and studies of a compound intended to be used as human or veterinary medicinal products and to facilitate the preparation of applications for marketing authorisations by the pharmaceutical industry. These guidelines have originally been published by the Commission in Volumes 3 and 7 of *"The rules governing medicinal products in the European Union"*.

Currently, new or updated guidelines are published by the EMA in the respective working party areas of its website.

3.3 Good Manufacturing Practice (GMP) Guidelines

In addition to the scientific guidelines in Volumes 3 and 7, Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC lay down the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use respectively. Detailed guidelines to interpret these principles and guidelines of GMP are published by the Commission in Volume 4 of *"The rules governing medicinal products in the European Union"*.

3.4 Maximum Residue Limits Guidelines

Council Regulation (EEC) No 2377/90, as amended, provides the legal framework for the establishment of maximum residue limits (MRLs) for medicinal products for veterinary use. Further guidance is provided in the Volume 8 of *"The rules governing medicinal products in the European Union"*. Guidelines on related specific issues are in addition published on the EMA website.

3.5 Pharmacovigilance Guidelines

Pharmacovigilance guidelines for medicinal products for both human and veterinary use are published in Volume 9 of *"The rules governing medicinal products in the European Union"*. For medicinal products for human use, such guidelines are drawn up by the European Commission in consultation with the EMA, Member States and interested parties in accordance with Article 106 of Directive 2001/83/EC as amended and Article 24 of Council Regulation (EEC) No 2309/93. For medicinal products for veterinary use the relevant articles are Article 77 of Directive 2001/82/EC as amended and Article 46 of Council Regulation (EEC) No 2309/93.

3.6 Good Clinical Practice (GCP) and conduct of clinical trial Guidelines

Specific provisions apply for good clinical practice for investigational medicinal products for human use. Directive 2001/20/EC is the framework legislation and provides for additional directives, accompanying guidelines and detailed guidance documents. These guidelines and guidance documents are expected to be published in *"The rules governing medicinal products in the European Union"*, Volume 10.

³ Formerly known as the Committee for Proprietary Medicinal Products (CPMP)

⁴ Formerly known as the Committee for Veterinary Medicinal Products (CVMP)

3.7 Orphan Medicinal Products Designation Guidelines

These guidelines are procedural regulatory guidelines relating to medicinal products for human use and published by the European Commission within the framework of Regulation EC No 141/2000 for instance in relation to the format and content of applications, on the following website: <http://pharmacos.eudra.org/F2/orphanmp/index.htm>. Scientific guidelines on aspects of orphan medicinal products are also prepared and published on the EMEA website.

3.8 Herbal medicinal products Guidelines

The Committee on Herbal Medicinal Products (HMPC) established by Regulation (EC) No 726/2004 and Directive 2004/24/EC is responsible for preparing scientific guidelines on aspects of herbal medicinal products development and these guidelines fall within the scope of this procedure.

The HMPC will also prepare a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products and establish Community herbal monographs.

This list of herbal substances, preparations and combinations thereof is excluded from the scope of the procedure for EU guidelines and related documents, as well as any Community herbal monograph drafted in the course of an application evaluation procedure. However, appropriate aspects of the procedure described in this document will be applied to the development of such monographs.

The Committee will also review the status and content of documents prepared by the Herbal Medicinal Products Working Party (HMPWP) between 1997 and 2004. The views presented in these documents were those of the HMPWP, which had been created as a forum for exchange of experience in the field of herbal medicinal products

3.9 Good Distribution Practice (GDP) Guidelines

Guidelines on GDP have been published by the European Commission in the Official Journal “C” series (94/C 63/03) and are published on the Commission’s website: <http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/may/GDPGuidelines1.pdf>. These guidelines have been prepared in accordance with Article 84 of Directive 2001/83/EC on the wholesale distribution of medicinal products for human use. They do not cover commercial relationships between parties involved in distribution of medicinal products nor questions of safety at work.

3.10 Good Laboratory Practice (GLP) Guidelines

When conducting non-clinical studies on chemical substances, marketing authorisation applicants are required to comply with Directive 2004/10/EC, which lays down the principles of good laboratory practice and refers to OECD guidelines. These OECD guidelines do not come within the scope of this procedure.

3.11 European Directorate for the Quality of Medicines (EDQM)⁵ and the European Pharmacopoeia

All monographs including general monographs and general chapters of the European Pharmacopoeia are applicable for the quality (chemical, pharmaceutical and biological) part of the dossier as prescribed in Directives 2001/83/EC, 2001/82/EC and 2003/63/EC. The EDQM has its own mechanism for consultation (Pharmeuropa and Pharmeuropa BIO) and the procedure described in this document does not apply.

In addition, and in order to facilitate the operation of the internal market, the European Directorate for the Quality of Medicines (EDQM), in collaboration with a panel of experts from the Official Medicines Control Laboratories (OMCLs), develops procedures and guidelines for the application of Official Control Authority Batch Release (OCABR) guidelines for the application of Article 114 of Directive 2001/83/EC. These are product specific and administrative guidelines, based on the monographs and general chapters and methods in the European Pharmacopoeia. They are intended to

⁵ The EDQM is the standardisation body of the nomenclatures and the quality norms within the meaning of the convention relating to the elaboration of the European Pharmacopoeia. This involves also resolution for certification of suitability, coordination of Official Medicines Control Laboratories (OMCL) network and development of standard terms.

be used by manufacturers and OMCLs for the quality control of medicinal products for human use derived from blood and for vaccines. EDQM has its own procedure for consultation (direct consultation with interested parties).

3.12 Other technical and procedural EMEA guidelines

The EMEA also publishes procedural and technical guidance and document templates e.g. (quality review of documents (QRD), pre-submission guidance, invented names, etc.... on its website. These do not come specifically within the scope of “*The rules governing medicinal products in the European Union*” but are intended to provide technical and procedural advice to applicants for marketing authorisations for medicinal products coming within the scope of the centralised procedure and are developed according to the principles outlined in this procedure.

3.13 Other related Community documents prepared/published by EMEA

The EMEA is responsible for preparing a large number of other public documents that cannot be considered as guidelines e.g. question and answer documents, public statements, reflection papers etc. To facilitate understanding, a non-exhaustive list of these documents, their definitions and a brief summary of their respective scopes can be found in section 6, The preparation of such documents does not follow the drafting procedure described in the next section.

4. PROCEDURE FOR DRAFTING A GUIDELINE

A guideline is normally developed in accordance with the following steps

1. *Selection of topic and inclusion in the relevant work programme(s)*
2. *Appointment of rapporteur and (if necessary) co-rapporteur*
3. *Development of concept paper*
4. *Adoption and release for consultation of concept paper*
5. *Preparation of initial draft guideline*
6. *Release for consultation of draft guideline*
7. *Collection of comments*
8. *Preparation of final version of guideline*
9. *Adoption of final guideline for publication*
10. *Implementation*

The steps and timelines referred to below represent standard practices. However in exceptional cases, the EMEA or the Commission reserves the right to omit certain steps or reduce timelines, with appropriate justification, where changes to guidelines are minor or the need for new or updated guidelines are particularly urgent. The justification for omission of steps will be made clear either in the published concept paper or as a cover note to the proposed text. Similarly if any deviation from the normal time for entry into force is envisaged, this will be addressed in the concept paper.

Comments received at steps 4 and 7 should be reviewed, and if necessary, critical comments should be discussed with experts and/or interested parties

The procedure outlined above may be terminated at or during any of the steps outlined to take account of new developments, changes in priorities or concerns raised during consultation. In these cases the concerned concept paper or draft guideline will be withdrawn and removed from the relevant work programme and an announcement published that it has been withdrawn or the work terminated. See also section 4.1 below.

4.1 Selection of topics and inclusion in EMEA work programme

The scientific committees and their working parties and the ad hoc GXP (GMP, GCP) inspection groups prepare a list of subjects upon which guidelines should be drafted for inclusion in the relevant work programme. Guidelines which may need to be reviewed and updated, stating the reasons for revision, are also listed.

Work programmes are continually reviewed, at least on an annual basis. The opportunity to cease work on topics included in the programmes may also be taken at time of review.

Input for guidelines for work programmes may also be received from the Member States, members of the scientific committees, within the framework of international activities as well as from interested

parties (e.g. the European pharmaceutical industry, European human and animal health professional groups, learned societies, patients' associations etc).

This input may be received at any time and/or may be prompted by any of the developments described under 4.1.1 to 4.1.3. Apart from the possibility to provide spontaneous suggestions in writing to the scientific committee chairs and EMEA secretariat, interested parties will be requested to provide their contributions in advance of the preparation of the annual work programmes, taking into account the timing of the relevant working party meetings.

In addition, legislative requirements, technical and scientific developments, international activities and requirements with respect to the operation of the internal market may necessitate the development of specific guidelines.

4.1.1 Legislative requirements

Within the framework of Community legislation, a delegation of power is given to the European Commission to prepare guidelines to elaborate on the practical operation of the legislation. These guidelines are generally prepared in consultation with the Member States, EMEA and interested parties. The European Commission may also delegate the drafting of these guidelines to the EMEA, e.g. scientific guidelines referred to in the Eudralex volumes. In the case where development of guidelines is mandatory, (e.g. when required by a specific piece of legislation) and/or for certain procedural guidelines, the steps related to the concept paper may be omitted.

4.1.2 Technical and scientific developments

The need for a new guideline may be triggered by frequently encountered problems with established products (e.g. clearer guidance on dossier requirements for certain indications/classes of products or harmonised requirements covering all EU Member States) or questions brought forward within the framework of scientific advice. Also, a need for a guideline may arise due to the development of new technologies, new practices or new therapeutic areas.

4.1.3 International activities

ICH: For human medicinal products, the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Steering Committee selects the topics for international harmonisation in accordance with its procedures. As appropriate, ICH topics are included in the work programme of the relevant CHMP working party or ad hoc group. Draft ICH guidelines are subject to EU-wide public consultation. Following Step 4 of the ICH procedure, the tripartite harmonised text is submitted to the CHMP or Pharmaceutical Committee for adoption. Once adopted by the CHMP, ICH guidelines have the same status as other European scientific guidelines and replace existing guidelines on the subjects covered. ICH guidelines may also be developed on subjects that do not come within the scope of scientific guidelines.

VICH: For veterinary medicinal products, the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products) Steering Committee select the topics for international harmonisation in accordance with its procedures. As appropriate, VICH topics are included in the work programme of the relevant CVMP working party. Draft ICH guidelines are subject to EU-wide public consultation. Following Step 7 of the VICH procedure, the agreed harmonised text is submitted to the CVMP for adoption. Once adopted by the CVMP, VICH guidelines have the same status as other European scientific guidelines and replace existing guidelines on the subjects covered. VICH guidelines may also be developed on subjects that do not come within the scope of scientific guidelines.

Cooperation with other regulatory authorities

In the framework of bilateral arrangements between the EU and other regulatory authorities, there may be a commitment to exchange information on work programmes, draft guidelines and/or other specific data. Input for new European guidelines may arise as a result of this collaboration.

4.1.4 Operation of the internal market

Where necessary and particularly for official batch release, the European Department for the Quality of Medicines (EDQM) and the network of Official Medicines Control Laboratories (OMCL) develop product specific guidelines to support Official Control Authority Batch Release (OCABR) of

medicinal products derived from blood and vaccines. The EDQM has its own mechanism for consultation (Pharmeuropa and Pharmeuropa BIO) and the procedure described in this document does not apply. See section 3.11.

4.2. Appointment of a rapporteur

Once a topic has been selected, a rapporteur (and co-rapporteur if appropriate) is appointed from the relevant working party, scientific advisory group, inspectors group or EMEA. In the case of a guideline prepared by a scientific committee, the relevant rules of procedure will apply to the appointment of rapporteur. Rapporteurs are responsible for drafting the concept paper and subsequent guidelines with the support of the relevant working party, group or committee.

4.3 Development of a concept paper

A concept paper is a public document which is primarily intended to convey the need for discussing specific issues, innovations or controversial key-points at any stage of the development of medicinal products with a view to laying down the foundation for future guidelines. A concept paper should point out the issues to be covered in the guideline, but should not elaborate already on solutions. However it may discuss possible options for a solution where these can already be identified or when reasonable.

- It should be a short document, of about 2 pages.
- It should contain:
 - Introduction
 - Problem statement
 - Discussion (on the problem statement)
 - Recommendation (s) (points to be addressed, including proposed objective and scope and options for solutions where possible)
 - Timetable for release of draft and final guidelines
 - Resource requirements for preparation
 - Impact Assessment:
(Anticipated impact on public and/or animal health and/or on the environment, anticipated benefit to industry, regulatory authorities and other interested parties, resource implications for its application by regulatory authorities and industry)⁶
 - If there are specific interested parties potentially affected by a particular topic, these should be identified by the rapporteur to ensure appropriate consultation. Other concerned EMEA working parties or groups should also be identified at this stage.
 - References to literature, guidelines, etc.
- It is for adoption by the Committee or GXP inspectors group
- Additional confidential information (e.g. from a registration dossier or from data received in a procedure of scientific advice) may be used to support the concept paper. This information will not be part of the published concept paper.

In the exceptional cases where a new guideline will apply to medicinal products already authorised and on the market, (see section 4.10), the reason why this is proposed will be stated.

Proposed deviations from the normal process should also be addressed, see introduction to section 4.

It should be noted that some guidelines come under the responsibility of more than one working party and/or scientific committee (multidisciplinary or joint guidelines). In these cases the EMEA secretariat ensures that the concept paper and draft and final guideline are discussed and agreed by all concerned working party/committees before adoption and publication.

4.4 Adoption and release for consultation of concept paper

Following adoption of the Committee or GXP inspectors group, concept papers are released for consultation to relevant interested parties through publication on the EMEA website for a period of 2-3 months, unless there is an urgent reason to accelerate the elaboration of a guideline, in the case of editorial changes, or where the proposed changes to an existing guideline are minor.

⁶ The extent and nature of this impact assessment will need to be adapted in accordance with the specific subject under discussion.

Specific procedures to ensure proactive and appropriate consultation of patients as well as disease specific patient organisations will be developed in conjunction with the EMEA/CHMP working group on patient organisations.

Similarly, provisions for appropriate consultation with health care professionals will be developed in the context of the EMEA's strategy for communication with health care professionals.

In response to specific justified concerns, where the underlying principles of the concept paper are questioned or challenged in a well-documented way, the EMEA may convene a meeting with relevant interested parties to discuss aspects of a concept paper.

Comments collected on the concept paper will be considered in the development of the future guideline, see below. Possible solutions for developing the guideline should be provided by interested parties, as part of the overall response to the concept paper. Preparation of the initial draft guideline may proceed in parallel to the consultation period, in particular where an issue of particular urgency is being addressed

Concept papers will normally not be revised as they are superseded by the draft and final guidelines respectively. Where there are concerns that critical comments received during the consultation process on the concept paper have not been taken into account in the drafting of a guideline, relevant comments may be resubmitted and, the reasons for not accepting them will be addressed in the public overview of the main comments.

If a concept paper does not develop into a final guideline or once a final guideline has been published, the concept paper is considered a historical document and will be archived. It will continue to be accessible in the "archived" section of the website. A decision not to progress a concept paper to a guideline shall be taken by the responsible committee or group.

Where appropriate, an explanation as to why specific concept papers do not progress to final guidelines will be made public.

4.5 Preparation of initial draft guideline

The rapporteur(s) prepares the draft text which should include a reference to existing EU directives and guidelines. Rapporteurs are also encouraged to identify the content and status of related guidelines in other regions. The draft text takes into account the comments received during the consultation period on the concept paper (if any). The rapporteur may consult appropriate experts to provide input.

The EMEA shall define the presentation style (template) to be used for preparing guidelines which shall include a table of contents.

The draft guideline should, where appropriate, contain, in addition to its scientific and technical content:

- Cover (title) page
- Table of contents
- Executive summary⁷
- Introduction (background)
- Scope
- Legal basis
- Proposed timetable⁸ (including timetable for discussion with other concerned working parties)
- Definitions
- References (scientific and/or legal and including a reference to the concept paper)

The scope should indicate whether the guideline concerns a selected area of medicinal product development where limited experience is available and knowledge is fast evolving, requiring the need for easy updates and flexibility.

⁷ See "New EMEA Transparency Policy Measures" 31 October 2003
<http://www.emea.eu.int/pdfs/general/manage/mbar/Transparency%20pol/005203en.pdf>

⁸ Customarily presented on the cover page of the guideline

This draft is considered by the relevant working party(ies)/ scientific advisory or inspectors group and as necessary, the rapporteur revises the draft text following each discussion in the working party and/or the written comments of the other members of the working party/group. It is also an opportunity for internal discussion by other working parties/groups indirectly concerned by the draft. During this process of elaboration of the draft text, the document is an internal paper of the relevant working party(ies).

Following consultation between the relevant working party chairs, the EMEA secretariat and the chairs of the concerned scientific committees, specific meetings may be organised with interested parties to provide input into or feedback on issues under discussion.

4.6 Release for consultation of draft guideline

When the text has been developed to a point where the views of the members of the working party/group are clearly presented, the draft guideline is submitted to the appropriate body (Scientific Committee/European Commission/European Pharmacopoeia) for adoption of the draft guideline for release for consultation.

When draft guidelines are released for consultation the cover page of the draft guidelines states that it is open for consultation and gives the date by which comments should be received.

Interested parties are encouraged to highlight inconsistencies of the proposed draft guidelines with related guidelines in other regions.

Normally draft guidelines are released for consultation for a period of 3 to 6 months.

To facilitate collection and review of comments, templates for submission of comments will be prepared. However other methods of providing comments will also be accepted.

Specific procedures to ensure proactive and appropriate consultation of patients as well as disease specific patient organisations will be developed in conjunction with the EMEA/CHMP working group on patient organisations.

Similarly, provisions for appropriate consultation with health care professionals will be developed in the context of the EMEA's strategy for communication with health care professionals.

4.7 Collection and treatment of comments

Depending on the subject, comments are expected from:

- Member States of the EEA/EFTA countries who gather and represent opinions from within that Member State
- Other regulatory authorities (e.g. FDA, Health Canada, Therapeutic Goods Administration, European Pharmacopoeia, other (V)ICH partners)
- European industry associations
- European scientific/academic societies and patients/consumer groups/health care professionals
- Other interested parties

Other regulatory authorities may be specifically encouraged to provide comments or other input.

Individuals are encouraged to comment via the relevant associations, societies or groups indicated above.

All comments received are carefully considered and discussed by the rapporteur and/or drafting group responsible for the guideline. They will systematically be published on the relevant website unless they contain commercially confidential information and/or the author has specifically objected to their publication.

If considered appropriate and in response to specific justified concerns or divergent views or upon request from interested parties, the EMEA may convene a meeting with relevant interested parties to discuss aspects of a draft guideline.

The rapporteur shall prepare an overview of the main comments which explains the rationale behind their acceptance or non-acceptance. This overview shall be made publicly available by the Agency, following agreement of the committee or group, as soon as possible, normally within 1 month of publication of the final text, taking into account meeting schedules.

Occasionally special circumstances may justify that an additional round of consultation may be used (in the event of extensive comments received during the first consultation period, necessitating a major revision).

4.8 Preparation of final version

Following the period of consultation, the comments received are considered by the working party. The text of the guideline is revised taking into account those comments considered relevant by the working party. The final text is submitted to the relevant scientific committee or other relevant group for adoption, together with a proposed date for implementation.

4.9 Adoption of final guideline

The committee and/or European Commission adopts the final guideline, depending on the type of guideline and the underlying legal requirements. The committees normally adopt guidelines at a plenary meeting, but may exceptionally use a written procedure.

The guideline is published on the relevant website and previous draft(s) and the concept paper are archived. The document reference number of the concept paper, draft guideline, final guideline and any revisions will facilitate tracking of evolving documents.

4.10 Implementation

Unless otherwise indicated, guidelines come into operation six months after their adoption. While applicants may, with the agreement of the competent authority concerned, choose to apply a guideline in advance of this period, competent authorities should wait until this period has expired before requiring the guideline to be taken into account.

In some circumstances it may not be possible for applicants to fully comply with new guidelines within this timeframe (e.g. data generated from trials started before the implementation of the new guideline). In such cases, the applicant should consider whether departure from the new guideline can be justified. The applicant's justification will then be considered on a case-by-case basis by the relevant competent regulatory authorities.

In exceptional circumstances, where it is in the interest of public and/or animal health and/or the environment, or to take account of specific legislative requirements and timeframes, a shorter period for implementation may apply (in such circumstances this will generally be announced at the consultation stage).

Guidelines are normally prepared for application prospectively. However, there may be exceptional situations in relation to risks to public and/or animal health where a guideline would need to be applied to medicinal products already authorised and on the market. In such circumstances, this would be announced at the consultation stage of the concept paper and draft guideline and will include an explanation as to the rationale. A clear statement to this effect will also be included in the final published guideline. In these instances, competent authorities will generally prepare a timetable for the application of the guideline to products on their market.

4.11 Training

Appropriate training in association with relevant working parties for assessors will be organised to ensure consistent application of guidelines. The competent authorities of the Member States are responsible for ensuring that assessors and experts possess adequate knowledge of the guidelines in their respective area. Subject to resource considerations joint training and workshops including representatives from interested parties may also be organised.

4.12 Maintenance and revision of adopted guidelines

The work programmes of the relevant working parties are reviewed at least on an annual basis. This provides an opportunity to review the continued applicability of existing guidelines and to take into account any feedback that may have been received. Suggestions for revision, updating or possible withdrawal of published guidelines are welcome at any time, but in particular in advance of preparation of the annual work programmes, see section 4.1. Normally guidelines will be considered for revision after five years of application. Where the scope of a guideline has indicated that there is

limited experience and knowledge is fast evolving, and/or major problems or major unanticipated changes in scientific knowledge come to light, review may be initiated earlier.

5. COMMUNICATION AND PUBLICATION

The EMEA and the Commission communicate information on any new developments, concept papers, adopted and draft guidelines under the “What’s new” sections of their respective websites.

“*The rules governing medicinal products in the European Union*” is the vehicle for publication of guidelines and legislation within the pharmaceutical legislative framework. Volumes 1, 2, 4, 6, 8 and 9 are published on the relevant European Commission website (<http://pharmacos.eudra.org>). All scientific guidelines in Volume 3 and 7, in addition to the scientific guidelines on the EMEA website are considered to be part of Volumes 3 and 7 respectively. The EMEA is working on a consolidation of existing texts and will publish the necessary links on its website. EMEA procedural and technical guidelines (see section 3.12) are also published on the EMEA website.

6. OTHER RELATED COMMUNITY DOCUMENTS PREPARED/PUBLISHED BY EMEA

To facilitate understanding, a non-exhaustive list of other related public documents prepared by EMEA, with a brief summary of their respective scopes is provided in this section. These do not follow the procedure for guideline preparation outlined in section 4 (concept paper, draft guideline, consultation, etc.).

6.1 Public statements

A public statement is a document, concerning a medicinal product / group of products or other topic related to medicinal products, which is issued in order to communicate information of importance to public and/or animal health. It is often (but not always) of an urgent nature (in particular concerning effective and safe use of a product(s) or informing of suspension / withdrawal of the product(s)). The statement is issued at European level by the EMEA and may also be used as a basis for public statements at national level.

6.2 Reflection Paper

A reflection paper may be developed to communicate the current status of discussions or to invite comment on a selected area of medicinal product development or a specific topic. It can provide a framework for discussion or clarification particularly in areas where scientific knowledge is fast evolving or experience is limited. A reflection paper does not provide scientific, technical or regulatory guidance, but may contribute to future development of such guidelines, or related documents.

6.3 Questions and Answer documents

The EMEA has developed “Questions and answers” or “Frequently asked questions (FAQ)” documents to provide additional public information on topics of particular interest. They are intended to briefly communicate, in easily comprehensible language, requirements, practices or interpretations responding to the most frequent questions in a specific area.

6.4 Compilation of Community Procedures on Inspections and Exchange of Information

This is a collection of guidelines applicable to all GMP Inspectorates in the EEA to facilitate harmonisation and collaboration. Article 3(1) of Directive 2003/94/EC requires the competent authorities to take account of the Compilation and this is achieved by using it to provide the basis for standard operating procedures within the quality management systems operated by the Inspectorates. Changes to the Compilation are agreed at the Ad Hoc GMP Inspection Services meetings and endorsed by the Pharmaceutical Committee established by Council Decision 75/320/EEC. The Compilation is published by EMEA on behalf of the Commission.

7. REFERENCES AND LINKS TO WEBSITES

EMA website: www.emea.eu.int

European Commission Pharmacos website <http://pharmacos.eudra.org/F2/eudralex/index.htm>

Volume 1 and 5 (Legislative texts): <http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm>

<http://pharmacos.eudra.org/F2/eudralex/vol-5/home.htm>

Volume 2 and 6 (*Notice to Applicants*) <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c>

<http://pharmacos.eudra.org/F2/eudralex/vol-6/home.htm>)

Volume 3 <http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm>

And 7 (Guidelines) <http://pharmacos.eudra.org/F2/eudralex/vol-7/home.htm>

Volume 4 (Good Manufacturing Practice): <http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm>

Volume 8 <http://pharmacos.eudra.org/F2/eudralex/vol-8/home.htm>

Volume 9 <http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm>

Good distribution practices:

<http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/may/GDPGuidelines1.pdf>.

Orphan medicinal products: <http://pharmacos.eudra.org/F2/orphanmp/index.htm>.

GLP directives: http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_050/l_05020040220en00280043.pdf

http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_050/l_05020040220en00440059.pdf

OECD: http://www.oecd.org/department/0,2688,en_2649_34381_1_1_1_1_1,00.html

Heads of Agencies: <http://heads.medagencies.org/>

Heads of Veterinary Agencies: <http://www.hevra.org/>

ICH: <http://www.ich.org>

VICH: <http://vich.eudra.org/>

WHO: <http://www.who.int/en/>

European Pharmacopoeia: <http://www.pheur.org/>

European Directorate for the Quality of Medicines: <http://www.edqm.org>