European Medicines Agency

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STATUS OF EMEA SCIENTIFIC GUIDELINES AND EUROPEAN PHARMACOPOEIA MONOGRAPHS AND CHAPTERS IN THE REGULATORY FRAMEWORK APPLICABLE TO MEDICINAL PRODUCTS

Executive summary

The present guideline clarifies the status of EMEA guidelines and European Pharmacopoeia monographs and chapters in the context of the regulatory framework applicable to medicinal products in the European Union.

1. Rules governing Medicinal Products in the European Union

The '*Introduction and general principles*' of Annex I of Directive 2001/83/EC[1], as amended, defines the principles governing the assurance of quality of medicinal products:

- (4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the **scientific guidelines** relating to the quality, safety and efficacy of medicinal products for human use as adopted by the [Committee for Medicinal Products for Human Use (CHMP)[2]] and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.
- (5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all **monographs including general monographs and general chapters** of the European Pharmacopoeia are applicable.
- (6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of **Good Manufacturing Practice** (GMP) for medicinal products for human use (2) and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.

Since Annex I of Directive 2001/83/EC, as amended, defines the detailed scientific and technical requirements for the marketing authorisation of medicinal products, these principles only apply to the evaluation of marketing authorisation applications and to authorised medicinal products.

These principles are also defined in the legislation governing veterinary medicinal products.

2. Role of EMEA scientific guidelines and European Pharmacopoeia monographs and chapters

EMEA scientific guidelines

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

[1] 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 (Official Journal L 311, 28/11/2001 p. 67 - 128), as amended.
[2] Previously called 'Committee for Proprietary Medicinal Products' (CPMP)

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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.

Within the framework of the pharmaceutical legislation, scientific 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, scientific 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[3].

European Pharmacopoeia monographs and chapters

The European Pharmacopoeia is a collection of standardised specifications on the quality of pharmaceutical preparations, their constituents or their containers. The European Pharmacopoeia covers but is not limited to: Synthetic chemical active substances; Natural products (e.g. herbal drugs, herbal preparations, herbal teas, essential oils, extracts); Biological products and biotechnology-derived products; Vaccines for human use; Veterinary vaccines; Mineral products; Radiopharmaceutical products; Excipients; Containers; Dosage forms; Homoeopathic preparations; Standard Terms on dosage forms, routes of administration and containers.

Some requirements may apply simultaneously to classes of substances and preparations and therefore are covered by general monographs and some requirements may be specific to a monograph dedicated to the substance/preparation in question.

Within the framework of the pharmaceutical legislation, monographs including general monographs and general chapters have legal force (see section 1 above) with regard to the quality part of the dossier supporting marketing authorisations unless the scope of the particular monograph or general chapter makes it clear that the text is not mandatory. The mandatory status of European Pharmacopoeia texts is explained in the *General Notices* of the European Pharmacopoeia.[4]

Furthermore, within the regulatory framework, reference to either the European Pharmacopoeia, the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia or the Japanese Pharmacopoeia is acceptable for products under development, for instance products undergoing clinical trials. For active substances, the suitability of the referenced monograph to adequately control the quality (impurity profile) will have to be demonstrated by the applicant/sponsor. Nevertheless, the need for later compliance with the European Pharmacopoeia to obtain a marketing authorisation should be taken into account during development to avoid difficulties during evaluation of the application for authorisation. Further information on this aspect is provided in the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004).

[3] 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. The mandatory requirement has been translated by the Ph. Eur. into the general monograph *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)*, which refers to the Note for guidance *verbatim*.

[4] The *General Notices (1.1)* of the Ph. Eur. state: "Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements. General chapters become mandatory when referred to in a monograph, unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information. (...) General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph." Furthermore, "Statements containing the word 'should' are informative or advisory" and the *General Notices (1.4)* specify those sections of a Monograph that constitute mandatory requirements and those that do not.

3. Complementary roles of EMEA scientific guidelines and European Pharmacopoeia monographs and chapters

Hence, EMEA scientific guidelines and European Pharmacopoeia monographs and chapters are complementary instruments to ensure the quality of medicinal products:

- guidelines provide advice on the best or most appropriate way to fulfil legal obligations
- the European Pharmacopoeia sets standardised specifications for pharmaceutical preparations, their constituents and containers.

For areas already covered by existing EMEA scientific guidelines, cross-references in European Pharmacopoeia texts to guidelines avoid repeating such guidance to facilitate updating. This is particularly important for new and rapidly evolving technologies for which guidelines may have to be amended frequently[5].

[5] The *General Notices (1.2)* of the Ph. Eur. state:"**References to regulatory documents**. Monographs and general chapters may contain references to documents issued by regulatory authorities for medicines, for example directives and notes for guidance of the European Union. These references are provided for information for users for the Pharmacopoeia. Inclusion of such a reference does not modify the status of the documents referred to, which may be mandatory or for guidance."