News bulletin for small and medium-sized enterprises

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This news bulletin is published by the SME Office of the European Medicines Agency. It will be published three times a year.

The news bulletin aims to bring to the attention of SMEs, and their stakeholders, documents and activities related to the European regulatory environment.

Inspections

A revised GMP (Good Manufacturing Practice) guide for human and veterinary use was published in February 2008 (Eudralex Volume 4). GMP part I, chapter 1 has been revised and a new annex 20 was added to implement ICH Q9 guideline on quality risk management, which becomes an integral part of a manufacturer's quality system. The new annex is however not intended to create any new regulatory requirements but rather provide an inventory of internationally acknowledged risk management methods with a list of potential applications at the discretion of manufacturers. It comes into operation in March (annex 20) and July 2008 (chapter 1).

A revised GMP guide on the "Manufacture of sterile medicinal products" (annex 1) was released in February 2008 following the completion of the public consultation (Eudralex Volume 4). It was revised to align the classification table for environmental cleanliness of clean rooms with ISO standards and provide guidance on the principles of GMP to sterile medicinal products. It was also updated to provide guidance on media simulations, bioburden monitoring and capping of freeze-dried vials. It will come into operation in March 2009 except for the provisions on capping of freeze-dried vials, which should be implemented by March 2010.

The following sections of the GMP guide were released in April 2008 for public consultation until 31 October 2008:

- Annex 11; GMP part I/chapter 4 on documentation on computerized systems (Links to Annex 11; GMP part I/chapter 4 on documentation) was updated in response to the increased use and complexity of computerised systems.
- GMP part II on basic requirements for active substances used as starting materials (Link to draft part II) was updated to include quality risk management of ICH guideline Q9.
- GMP annex 13 on investigational medicinal products (Link to annex 13) was updated to clarify points on reference and retention samples, the two-step release procedure for investigational medicinal products and the principle of independence between production and quality control functions.

The Good Manufacturing Practice (GMP) questions & answers page was also updated in February 2008 (GMP questions & answers).

Scientific guidelines for human medicines

Quality

A reflection paper on water for injection prepared by reverse osmosis was released in March 2008 (EMEA/CHMP/CVMP/QWP/28271/2008). It outlines in view of recent technological advancements in this field why it is currently not considered acceptable to use reverse osmosis for the preparation of water for injection. The paper also applies to *veterinary medicines*.

Non-clinical safety

A questions and answers (Q&A) document on the CHMP guideline on the limits of genotoxic impurities was released in January 2008 (EMEA/CHMP/SWP/431994/2007).

A guideline on the non-clinical development of fixed combinations medicinal products was published in January 2008 (EMEA/CHMP/SWP/258498/2005). It provides guidance on non-clinical development strategies based on available data to support safe human use and avoid unnecessary animal studies. It applies to fixed combinations of chemically defined substances, biological substances or of herbal substances/herbal preparations. The guideline may also be considered for combination therapy not involving a fixed combination formulation. It will come into effect in August 2008.

A draft non-clinical guideline on drug-induced hepatotoxicity was released in March 2008 (EMEA/CHMP/SWP/150115/2006). Its objective is to provide guidance on how to handle non-clinical signs of drug-induced hepatotoxicity in order to decrease the risk of clinical adverse liver reactions for systemically absorbed medicinal products (cytotoxic anti-cancer medicinal products are exempted from this guideline). It is released for consultation until 30 August 2008.

A guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications was released in March 2008 (EMEA/CHMP/SWP/169215/2005). Its objective is to advise on the need, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use. It applies to initial medicinal products applications and authorised medicinal products developed in paediatric indications. The guideline does not apply to vaccines. It will come into effect in August 2008.

A draft on repeated dose toxicity was released in March 2008 (EMEA/CHMP/SWP/488313/2007). It aims to provide guidance on the conduct of repeated dose toxicity studies of active substances intended for human use (including herbal medicines). It does not apply to biotechnology-derived compounds, vaccines and anticancer medicinal products.

A guideline on the specification limits for residues of metal catalysts or metal reagents was released in March 2008 (EMEA/CHMP/SWP/4446/2000). Its objective is to recommend maximum acceptable concentration limits for the residues of metal catalysts or metal reagents used during the synthesis of pharmaceutical substances and which may be present in pharmaceutical substances (active ingredient or excipient) or in drug products. It will come into effect in September 2008.

An ICH guideline on genotoxicity testing and data interpretation for pharmaceuticals intended for human use was released in April 2008 (EMEA/CHMP/ICH/126642/2008). The guideline was revised to promote the reduction of use of animals in genotoxicity testing.

Clinical efficacy and safety

A questions and answers (Q&A) document on the use of "cocktail" studies for investigating in vivo drug interaction potential was released in January 2008 (EMEA/CHMP/EWP/490784/2007).

"Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man/methodological considerations for using progression-free survival (PFS) as primary endpoints in confirmatory trials for registration" was released in February 2008 (EMEA/CHMP/EWP/27994/2008). It provides guidance on issues to prospectively consider relating to definitions, frequency and methods of assessment, ascertainment bias, handling of deviations and missing data, and radiology review. It will come into effect in August 2008.

A draft guideline on fixed combination medicinal products was released in March 2008 (CPMP/EWP/240/95 Rev. 1). It covers the development of fixed-combination medicinal products containing two or more active substances, considering the intended use and indication.

A CHMP reflection paper on benefit-risk assessment methods in the context of evaluation of marketing authorisation application of medicinal products for human use was released in March 2008 (EMEA/CHMP/15404/2007).

A guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins came into effect in April 2008 (EMEA/CHMP/BMWP/14327/2006). It contains information on the potential causes of immunogenicity and advice on the immunogenicity evaluation from a marketing authorisation perspective.

Advanced therapies

Revised Part IV, Annex I to Directive 2001/83/EC was released in April 2008 (Link). Regulation (EC) No 1394/2007 on advanced therapy medicinal products lays down specific requirements for advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue engineering). It will apply from 30 December 2008. The implementation plan of the regulation includes the revision of Part IV, Annex I to Directive 2001/83/EC in order to adapt it to the specificities of advanced therapy medicinal products. It is released for consultation until 10 June 2008. In addition a public consultation document outlining preliminary proposals to establish provisions for the evaluation and certification of quality and, where available, non-clinical data, for advanced therapies was published in May 2008 (Link). The document is released for public consultation until 4 July 2008.

Small and Medium-sized Enterprises (SMEs) involved in advanced therapy medicinal products are particularly welcome to provide comments.

Regulatory guidance for human medicines

A document on the scientific aspects and working definitions of the mandatory scope of the centralised procedure was released in January 2008 (EMEA/CHMP/121944/2007). It aims at clarifying which therapeutic indications fall within the mandatory scope of the centralized procedure for Marketing Authorisation Applications evaluation (Annex to Regulation (EC) No 726/2004). It will come into effect in May 2008.

A final guideline on the acceptability of invented names for medicinal products processed through the centralised procedure was released in January 2008 (CPMP/328/98 Revision 5). It aims to provide guidance on the criteria applied by the EMEA when reviewing the acceptability of the proposed names for medicinal products processed through the centralised procedure.

Annexes 1, 2 and 3 (Clinical Trial Application Form, Substantial Amendment Form and Declaration of the end of a Clinical Trial Form) of the 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial' were released in February 2008 (Revised annexes). The annexes were revised to take into consideration Regulation (EC) No 1901/2006 on medicines for paediatric use, the guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) and clarify the submission of information on the results of clinical trials in view of its publication.

Information on the EMEA implementation of electronic-only submissions and eCTD submissions in the centralised procedure was released in February 2008 as follows:

- EMEA implementation of electronic-only submissions and eCTD submissions in the centralised procedure: Statement of Intent (EMEA/563366/2007)
- Questions and answers relating to strategic and general aspects of the implementation (EMEA/596870/2007 correction)
- Questions and answers relating to practical and technical aspects of the implementation (EMEA/596881/2007 v0.2)

An updated version of questions & answers of volume 2B of the notice to applicants was released in March 2008 (Questions & Answers link). It addresses frequently asked implementation questions relating to the presentation and format of the dossier/common technical document (CTD).

An updated version of questions & answers on volume 9A relating to pharmacovigilance implementation was released in April 2008 (Questions & Answers link). It addresses frequently asked implementation questions and provides conventions for the harmonised interpretation of volume 9A of the rules governing medicinal products in the European Union: pharmacovigilance for medicinal products for human use.

Scientific guidelines for veterinary medicines

A VICH topic GL45: bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products ((EMEA/CVMP/VICH/581467/2007) was released in February 2008. It provides guidance on bracketing and matrixing study designs and defines principles for situations in which bracketing or matrixing can be applied. It is released for consultation until 11 August 2008.

A VICH topic GL24 step 4 pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs) was released in March 2008 (EMEA/CVMP/VICH/547/00). The scope of pharmacovigilance is defined in this guidance as the management of the detection and investigation of the clinical effects of marketed veterinary medicines concerned with the safety and efficacy in animals and the safety in people exposed to these products. The date of coming into operation will be determined at a later stage.

Regulatory guidance for veterinary medicines

A guideline on the acceptability of names for veterinary medicinal products processed through the centralised procedure was released in February 2008 (EMEA/CVMP/328/98 Revision 3). It provides guidance on the procedure and criteria applied when reviewing the acceptability of the proposed names for medicinal products processed through the centralised procedure.

Fees

Updated rules for the implementation of Regulation (EC) No 297/95 as amended on fees payable to the EMEA were released in April 2008 (EMEA/MB/140377/2008). Further guidance on the new fees payable to EMEA can be found here.

Workshops

The presentations from the 2nd EMEA Workshop for SMEs "Focus on Quality" which took place in 8 February 2008 were published (Link). The objective of the workshop was to provide an overview of data requirements for authorisation of new chemical entities and biologicals, highlighting key success factors and practical advice from an EU assessors' perspective. Presentations also included highlights from recent scientific advice and protocol assistance, GMP compliance, "Quality by design" and the regulation on advanced therapies.

The presentations from the EMEA/ICH Workshop on Viral/Vector Shedding which took place on 30 October 2007 have been published (Link).

A report on the EMEA-EFPIA Joint Workshop on Adaptive Designs in Confirmatory Clinical Trials which took place on 14 December 2007 has been published (Link).

SME companies registered with the EMEA

274 companies currently have SME status assigned by the EMEA. The list of companies is published on the EMEA website at: http://www.emea.europa.eu/pdfs/SME/registeredcompanies.pdf

Contact the SME Office

The SME Office has been set up within the Agency to address the particular needs of smaller companies. The Office aims to facilitate communication with SMEs through dedicated personnel who will respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs. Any comments on this news bulletin can be forwarded to the SME Office:

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