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.

Advanced Therapies

A guideline on follow-up of patients administered with gene therapy medicinal products was released on 18 June 2008 (EMEA/CHMP/GTWP/60436/2007). It outlines recommendations for clinical monitoring and follow-up after treatment with gene therapy medicinal products to detect early signals of delayed adverse reactions, prevent clinical consequences of such reactions and gather long-term safety and efficacy data. The principles included in this guideline are applicable for patients enrolled in clinical trials using gene therapy medicinal products and administered with authorised gene therapy medicinal products. It is released for consultation with a deadline for comments by 30 November 2008.

A guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products was released on 18 June 2008 (EMEA/CHMP/GTWP/125491/2006). It sets out the scientific principles and methodology for the environmental risk assessment of gene therapy GMO-containing medicinal products for human use required for centralised marketing authorisation. It also provides guidance on the methodology included in Directive 2001/18/EC on the deliberate release of genetically modified organisms into the environment. It will come into effect on 30 November 2008.

A guideline on non-clinical studies required before first clinical use of gene therapy medicinal products was released on 18 June 2008 (EMEA/CHMP/GTWP/125459/2006). It defines scientific principles and provides guidance on the non-clinical studies required for these specific products. It will come into effect on 30 November 2008.

A special announcement was released by the EMEA on 1 July 2008 to manufacturers, companies and hospitals having advanced therapy medicinal products legally on the EU market in accordance with national or EU legislation (EMEA/326145/2008). It reminds sponsors that these products will have to undergo a marketing authorisation procedure through the EMEA. The review process will follow the normal procedure for the centralised procedure for advanced therapy medicinal products and exemptions may apply to some products.

A draft guideline on good clinical practice (GCP) for advanced therapy medicinal products was released by the European Commission on 4 July 2008 (Link). The regulation on advanced therapy medicinal products (Regulation (EC) No 1394/2007) will apply from 30 December 2008. Article 4 of this Regulation requires the development of specific guidelines on good clinical practice (GCP) for advanced therapy medicinal products. It is released for consultation until 15 October 2008.

A guideline on human cell-based medicinal products was released on 21 May 2008 (EMEA/CHMP/410869/2006). It provides guidance on the quality/manufacturing, non-clinical pharmacology/toxicology, pharmacodynamic/ pharmacokinetic, dose finding, clinical efficacy and safety studies, including pharmacovigilance and risk management. It will come into effect on 1 September 2008.

Pharmacogenomics

A reflection paper on pharmacogenomics in oncology was released on 6 May 2008 (EMEA/CHMP/PGxWP/128435/2006). It outlines the impact of pharmacogenomic/pharmacogenetic information on the regulatory process in oncology with emphasis on the information to be included in the product literature.

A final ICH concept paper on "Pharmacogenomic (PG) biomarker qualification: Format and data standards" was released on 25 June 2008 (EMEA/CHMP/190395/2008). It supports the proposal for a new harmonized ICH guideline on the qualification of pharmacogenomic biomarkers. The guideline intends to provide recommendations on the collection of data to support the qualification of pharmacogenomic biomarkers, how to define the qualification context and the claims for intended use, standard methods for data collection and formats for submission of data to regulatory authorities.

Guidance on Pharmaceutical Development

An update of the questions and answers document from the EMEA Quality Working Party was published on 30 July 2008 (Link). It was updated to include clarifications on the chapter "Ph. Eur. chapter uniformity of dosage units".

A guideline on the quality of biological active substances produced by stable transgene expression in higher plants was released on 11 August 2008 (EMEA/CHMP/BWP/48316/2006). It provides guidance on the approaches to achieve quality for substances produced with this new technology. It will come into effect in February 2009.

A guideline on virus safety evaluation of biotechnological investigational medicinal products was released on 11 August 2008 (EMEA/CHMP/BWP/398498/2005). It provides guidance on viral safety evaluation studies required prior to and during clinical development. It will come into effect in February 2009.

ICH Topic Q 10 Note for Guidance on Pharmaceutical Quality System was released on 24 July 2008 (EMEA/CHMP/ICH/214732/2007). Manufacturers in the EU are obliged to establish an effective pharmaceutical quality assurance system in order to comply with Good Manufacturing Practice (GMP). Guidance is provided in Chapter 1 of the GMP Guide (Link). ICH Q10 provides an example of a pharmaceutical quality system designed for the entire product lifecycle. It should be noted that ICH Q10 is optional but should facilitate innovation, continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

The following annexes to ICH Topic Q4B were released on 27 June (Annexes 2, 3 and 4) and 24 July 2008 (Annexes 4A, 4B and 4C):

- Annex 2 to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for extractable volume of parenteral preparations" (EMEA/CHMP/ICH/559409/2007). It will come into effect in December 2008.
- Annex 3 to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for particulate contamination: sub-visible particles" (EMEA/CHMP/ICH/561176/2007). It will come into effect in December 2008.
- Annex 5 to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on disintegration test" (EMEA/CHMP/ICH/308895/2008). It will come into effect in September 2008.
- Annex 4A to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on microbiological examination of non-sterile products: microbial enumeration tests" (EMEA/CHMP/ICH/308671/2008). It will come into effect in September 2008.
- Annex 4B to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for microbiological examination of non-sterile products: tests for specified micro-organisms" (EMEA/CHMP/ICH/308817/2008). It will come into effect in September 2008.

- Annex 4C to "Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use" (EMEA/CHMP/ICH/308867/2008). It will come into effect in September 2008.

A guideline on stability testing of existing active substances and related finished products for *veterinary* medicines was released on 8 August 2008 (EMEA/CVMP/QWP/846/99-Rev.1). It will come into effect in September 2011.

Guidance on Non-Clinical Development

An ICH guideline on dose selection for carcinogenicity studies of pharmaceuticals was released on 6 May 2008 (ICH S1 C (R2); EMEA/CHMP/ICH/383/1995). It will come into effect in October 2008. Carcinogenicity studies for chemical agents rely generally on the maximally tolerated dose (MTD) as the standard method for high dose selection, on the basis of data from 3-month toxicity studies. The guidance aims at harmonising requirements for high dose selection for carcinogenicity studies and outlines the criteria for dose selection to provide greater flexibility in optimising the design of carcinogenicity studies (e.g. maximum tolerated dose, 25-fold AUC ratio (rodent/human), dose-limiting pharmacodynamic effects, saturation of absorption, maximum feasible dose, limit dose, pharmacodynamic-, pharmacokinetic-, toxicity-based endpoints).

A revised question and answer on the CHMP guideline on the limits of genotoxic impurities was released on 5 July 2008 (EMEA/CHMP/SWP/431994/2007). It provides clarifications on the guideline (EMEA/CHMP/QWP/251344/2006) published in 2006.

A guideline on "Risk assessment of medicinal products on human reproduction and lactation: from data to labelling" was released on 5 July 2008 (EMEA/CHMP/203927/2005). It describes the process of assessment of (non)clinical data and the link between the assessment of these data and the labelling of a medicinal product. It will come into effect in January 2009.

A revision of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals was released on 30 July 2008 (M 3 (R2); CPMP/ICH/286/95). It recommends international standards for harmonising the non-clinical safety studies to support human clinical trials and marketing authorization. It is released for consultation until October 2008.

Guidance on Clinical Development

Guidance to applicants on biomarkers qualification was released on 19 May 2008 (EMEA/CHMP/SAWP/72894/2008). The EMEA qualification process is a new, voluntary, scientific pathway leading to two main types of Scientific Advice on innovative methods or drug development tools a) Qualification Advice on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development setting (non-clinical or clinical studies) based on the *assessment* of data b) Scientific Advice on *future* protocols and methods for further method development towards qualification based on the evaluation of the scientific rationale and on preliminary data submitted.

An ICH Topic E 14 questions and answers on the clinical evaluation of QT/QTs interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs was released on 27 June 2008 (EMEA/CHMP/ICH/310133/2008).

An ICH Topic E 2F note for guidance on "Development safety update report" (DSUR) was released on 27 June 2008 (EMEA/CHMP/ICH/309348/2008). The DSUR is intended to be the common standard for annual clinical trial safety reporting among the ICH regions and could be submitted instead of existing reports including the US IND Annual Report and the EU Annual Safety Report. It is released for consultation until December 2008.

Paediatrics

New legislation governing the development and authorisation of medicines for use in children was introduced in the European Union in January 2007. Regulation (EC) No 1901/2006 introduced major changes into the regulatory environment for paediatric medicines, designed to better protect the health of children in the EU. A report from the Paediatric Committee on its first anniversary was released on 11 July 2008 (Link). It includes details about the Committee's core activities i.e. the review of Paediatric investigation plans and waivers, the Committee's regulatory activities and the cooperation with other EMEA committees, Member States and Learned Societies. Sponsors are reminded that as of 26 July 2008 marketing authorisation applications (MAA) for new medicinal products are subject to compliance check at time of submission of the MAA (Link). Any questions from future MAA applicants should be directed to paediatrics@emea.europa.eu. Further information about the Paediatric Initiative is available on the EMEA website (Link).

Inspections

Revised 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 finalised and published on 26 June 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 and clarify the submission of information on the results of clinical trials for publication.

Regulatory Guidance for Human and Veterinary Use

A new regulatory and procedural guidance section of EMEA website was created to provide easy access to regulatory and procedural guidance relevant for the centralised procedure (Link). It includes pre- and post-authorisation guidance, the recently published procedural advice for centralised generic/hybrid applications (EMEA/CHMP/225411/2006), and updated procedural advice for orphan medicinal product designation (EMEA/14222/00/Rev 4; EMEA/357465/2008/Rev 3)

Updated versions of Notice to Applicants/Volume 2B, 2C and 6A were released in May and June 2008. They include new sections relating to paediatrics, updated versions of the application form for variation to mutual recognition/decentralised/centralised procedure marketing authorisation for human and veterinary medicines (Link).

Scientific Advice for Veterinary Medicines

General principles for parallel scientific advice meetings were published in May 2008 (Link). The EMEA and FDA initiated a pilot programme to provide parallel scientific advice in 2004-5. The goal of this pilot phase was to provide a mechanism for EMEA and FDA assessors and sponsors to exchange their views on scientific issues during the development phase of new veterinary medicinal products (i.e. new veterinary drugs, maximum residue limits). This programme of co-operation in the field of scientific advice will continue in 2008-2009. Further information on Scientific Advice can be found in http://www.emea.europa.eu/htms/vet/genguidance/sciadvice.htm.

Report from Meetings

The presentations from the EMEA-EFPIA workshop on adaptive designs in confirmatory clinical trials which took place on 14 December 2007 are available on the EMEA website (Link).

SME companies registered with the EMEA

314 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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