EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

News bulletin for small and medium-sized enterprises

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This news bulletin is published four times a year by the SME Office of the European Medicines Agency.

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

IN THIS ISSUE:

Guidance on quality of medicines

A draft reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems was released on 13 October 2010 (EMA/CHMP/QWP/574767/2010). It provides information on the pharmaceutical development and characterisation of products such as:

- medicinal products for intravenous injection or infusion which contain active substances with a low aqueous solubility and solubilised in an aqueous micellar system;
- established small molecule, non-polymeric surfactants, which are sensitive to dilution effects during slow intravenous administration, quickly metabolised and which therefore do not have a long half-life in plasma e.g. polysorbate 80.

The document is released for consultation until end of December 2010.

The following annexes to ICH guideline Q4B have been released. They recommend that the analytical procedures described in the official pharmacopoeial texts (Ph.Eur., JP, USP) can be used interchangeably in the ICH regions:

- *'Annex 11 of the Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Capillary Electrophoresis – General Chapter - Step 4'* (EMA/CHMP/ICH/730028/2009). It came into effect in December 2010.
- *'Annex 12 of the Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Analytical sieving – General Chapter - Step 4'* (EMA/CHMP/ICH/730808/2009). It came into effect in December 2010.
- *'Annex 13 of the Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bulk Density and Tapped Density of Powders – General Chapter - Step 3'* (EMA/CHMP/ICH/405290/2010). It is released for consultation until end of December 2010.
- *'Annex 14 to Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bacterial Endotoxins Tests – General Chapter - Step 3'* (EMA/CHMP/ICH/529785/2010). It is released for consultation until end of December 2010.

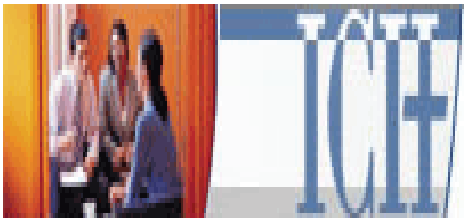
Clinical guidance

A guideline on missing data in confirmatory clinical trials was adopted on 20 September 2010 (EMA/CPMP/EWP/1776/99 Rev.1). It provides advice on how such data in pivotal clinical trials should be addressed and reported in a dossier submitted for regulatory review. It focuses on the analysis of the primary efficacy endpoint where patients are followed up over time and addresses how patients withdrawing should be considered. The principles included in the document apply to superiority, non-inferiority and equivalence trials. It will come into effect in January 2011.

A draft guideline on the clinical investigation of medicinal products intended for the treatment of chronic obstructive pulmonary disease (COPD) was adopted on 20 September 2010 (CPMP/EWP/562/98 Rev. 1). It includes guidance on the clinical evaluation of new medicinal products for the treatment of COPD, new products which may provide symptomatic relief through improvement of airway obstruction, modify or prevent exacerbations, modify the course of the disease or modify disease progression. The document is a revision of the *'CPMP Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) CPMP/EWP562/98'*. It is released for consultation until 1 March 2011.

Draft guidance for laboratories that perform the analysis or evaluation of clinical trial samples was adopted on 23 September 2010 (EMA/INS/GCP/532137/2010). It provides these bodies with information that will help them develop and maintain quality systems complying with EU directives, regulations and National guidance documents. It also includes information on the expectations of inspectors who may inspect facilities that perform work in support of human clinical trials. It is released for consultation until 28 February 2011.

An ICH guideline *'E2F: Note for guidance on development safety update reports (DSUR) - Step 4'* was adopted on 24 September 2010 (EMA/CHMP/ICH/309348/2008). The DSUR is intended to be a common standard for periodically reporting on the safety of medicines under development (including marketed drugs that are under further study) in the ICH regions. Submitted annually, it would meet national and regional requirements currently met by the US IND Annual Report and the EU Annual Safety Report and can therefore replace these. The ICH guideline defines the content and format of a DSUR and provides advice on its preparation and submission. It will come into effect in September 2011.



An ICH guideline *'E16 Genomic biomarkers related to drug response: context, structure and format of qualification submissions - Step 4'* was adopted on 24 September 2010 (EMA/CHMP/ICH/380636/2009). Its scope includes qualification submissions for clinical and non-clinical genomic biomarkers related to the development of chemicals or biotech products including translational medicine approaches, pharmacokinetics, pharmacodynamics, efficacy and safety aspects. A qualification submission can include data and claims for a single or multiple genomic biomarkers. The principles described in the ICH guidance are also applicable to non-genomic biomarker categories (e.g. proteomics, imaging) while a qualification submission for a combination of biomarkers (e.g., genomic and non-genomic) is possible too. The aim of having a consistent format for submission of biomarker data is to improve evaluation of current biomarkers and facilitate exchange of assessments between regions. It is released for consultation until 1 March 2011.

A revised guidance *'EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)'* was adopted on 22 October 2010 (EMA/H/20665/04/Final Rev. 2). It includes new validation rules for safety message processing and message acknowledgment implemented in EudraVigilance. It is applicable to all stakeholders which are exchanging such information electronically within the EEA. Based on the experience gained since the previous version of the guidance, new validation rules and mandatory data elements from ICH E2B(R2)2 should be applied to all ICSRs exchanged within the EEA. They are relevant to all ICSRs which qualify for expedited and periodic reporting and originating within or outside the EEA. The new validation rules and mandatory ICH E2B (R2) data elements should be implemented as outlined in the detailed Implementation plan (EMA/665231/2008 – Revision 1).

Guidance on biologics

Guidance documents on the Agency's new certification procedure for advanced therapies were released on 10 November 2010 (EMA/CAT/418458/2008/corr, EMA/CAT/486831/2008/corr). Small and Medium-sized Enterprises (SMEs) developing advanced therapy medicinal products (gene therapy, cell therapy, tissue engineering products) may submit pharmaceutical/quality and where available preclinical/non-clinical data generated during development to the EMA for scientific evaluation and certification. The certificate may be issued following the submission of a request which is evaluated scientifically. The documents provide guidance to applicants on the dossier content, the procedure for submission, evaluation and the issuance of the certificate. Companies interested in this new procedure are advised to contact the SME Office.

The following guidance documents on monoclonal antibodies were released on 26 November 2010:

- Biosimilar medicines containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). It complements the general biosimilar guideline (EMEA/CPMP/42832/05) with specific aspects on monoclonal antibodies. Its principles may also be relevant for substances such as fusion proteins based on IgG Fc (-cept substances).
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010). It includes and addresses issues such as the variability in immunogenicity of these products, its prediction and minimization.

Both documents are released for consultation until 31 May 2011.

Veterinary guidance

A draft guideline on statistical principles for veterinary clinical trials was released on 27 September 2010 (EMA/CVMP/EWP/81976/2010). It provides guidance on the statistical principles to be considered in the design, conduct, analysis and evaluation of clinical trials to demonstrate efficacy and/or safety of an investigational veterinary pharmaceutical product. The guideline is similar to its counterpart in the human field (Note for Guidance on Statistical Principles for Clinical Trials-CPMP/ICH/363/96) and addresses specific veterinary issues. It also details a number of issues relating to hypothesis testing (superiority, non-inferiority), confidence intervals for response variables, power calculations and other statistical methods identified by regulators in recent years. It is released for consultation until 31 March 2011.

A *'VICH GL42: Data elements for submission of adverse event reports'* was released on 27 September 2010 (Link). It describes the specific data elements to be used for the submission and exchange of spontaneous adverse event reports for veterinary medicinal products between marketing authorisation holders and regulatory authorities. The guidance should be read in conjunction with the definitions given in VICH GL24 (Management of Adverse Event Reports). For the purpose of electronic reporting, it should be read in conjunction with:

- 'VICH GL30: Guideline controlled lists of terms' released on 27 September 2010 (Link).
- 'VICH GL35: Guideline on pharmacovigilance of veterinary medicinal products: electronic standards of data' released for consultation until 15 March 2011.on 27 September 2010 (EMA/CVMP/VICH/123940/2006).

A guideline on requirements for including a substance in the list of substances considered as falling outside the scope of the maximum residue limit ('MRL') Regulation (EC) No 470/2009 was released on 18 November 2010 (EMA/CVMP/516817/2009). It will come into effect in June 2011.

Regulatory guidance

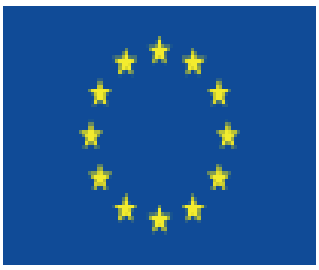
Information on the new fees payable to the EMA was released on 11 October 2010 (EMA/348317/2010; EMA/MB/818152/2009). The revised rules include new, reduced fees for the third and subsequent type-II variations in a grouping or work-sharing application, and for additional strengths or potencies of the same pharmaceutical form in an application for an extension of marketing authorisation. The revision also includes amendments to the fees for grouped variations to plasma and vaccine antigen master files and to annual fees.

Draft guidance was released on 11 October 2010 on *'Procedural aspects and dossier requirements for the consultation to the EMA by a notified body on an ancillary medicinal substance or an ancillary human blood derivate incorporated in a medical device or active implantable medical device'* (EMA/CHMP/578661/2010 Rev 1). It details procedural, format and data requirements to facilitate the consultation procedure to the EMA by notified bodies on ancillary medicinal substances and ancillary human blood derivatives. The document applies to any application for consultation submitted to the Agency by notified bodies. It is released for consultation until 31 January 2011.

A draft reflection paper on the designation of enantiomers as new active substances was released on 23 November 2010 (EMA/651649/2010). It provides details on evidence that would be required to support the designation of a single stereo isomeric form (enantiomer) as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers. The document is intended to provide advice on aspects related to data exclusivity, data requirements and access to the centralised procedure. It is released for consultation until 28 February 2011.

News from the European Commission

New EU pharmacovigilance legislation was adopted by the European Parliament on 22 September 2010. The new Directive and Regulation propose a number of major changes that will strengthen the way the safety of medicines for human use is monitored in the European Union. This will include an enhanced monitoring of the benefits and risks of medicines post-authorisation, a replacement of the Pharmacovigilance Working Party with a new EMA Committee, and an increased level of transparency on the safety of medicines. The legislation will come into force in 2012 and implementation of the new legislation will start at the Agency in 2011.



A revised chapter 7 of the 'Volume 4-Good Manufacturing Practice' laying down the detailed guidelines for outsourcing activities was released on 9 November (Link). It was revised to provide guidance on outsourced activities beyond the current scope of contract manufacture and analysis operations, in line with the ICH Q10 guideline on the Pharmaceutical Quality System. It is released for consultation until 28 February 2011.

The Questions and Answers document in the EudraLex chapter on clinical trials has been revised (Link).

The production of EudraCT Version 8.0 has been delayed. As a result, Revision 4 dated November 2009 of the '*Clinical Trials Application Form'* will **not** apply for the time being. For more information please refer to the EudraCT and EC websites.

Meetings

The following meetings have been announced:

- 'Availability of veterinary medicines: providing a climate for science and innovation', European Medicines Agency, London, 23-24-March 2011 (Link)
- Second international symposium on biopharmaceutical statistics, Berlin, 1-3 March 2011 (Link)

Reports from the following meetings were released:

- Workshop on paediatric formulations for assessors in national regulatory agencies held 31 May 2010 (Link)
- Workshop on nanomedicines held on 2-3 September 2010 (Link)
- The video casts of the workshop on stem cells are now available under Link.

SME companies registered with the Agency

507 companies currently have SME status assigned by the Agency. Information on the companies are published on the Agency's website at: SME office

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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