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SME Office NEWSLETTER

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IN THIS ISSUE

Pharmaceutical development guidance

Two annexes to ICH guidance Q4B which recommend that analytical procedures described in the official pharmacopoeial texts can be used interchangeably in the ICH regions were announced on:

- Bulk density and tapped density of powders (EMA/CHMP/ICH/405290/2010), which will come into effect in January 2013.
- Bacterial Endotoxins (Ph.Eur.2.6.14. Bacterial Endotoxins, JP 4.01 Bacterial Endotoxins Test, and USP General Chapter <85> Bacterial Endotoxins Test) (EMA/CHMP/ICH/529785/2010). It will come into effect in May 2013.

A draft guideline on the pharmaceutical development of medicines for paediatric use was released for consultation (EMA/CHMP/QWP/805880/2012 Rev. 1). Specific sections of the document on e.g. handling of oral solid preparations to facilitate administration, mixing with food and drinks and patients acceptability were revised following a first round of consultation. The guideline is now open for further comments until 1 April 2012.

A draft guideline on the use of porcine trypsin in the manufacture of human biologics was released for consultation until 31 August 2013 (EMA/CHMP/BWP/814397/2011). Porcine trypsin is a reagent widely used in the manufacture of vaccines and recombinant proteins. It is extracted from the pancreas of pigs, and carries the risk of contamination with adventitious agents such as viruses.

A draft ICH guidance on the photosafety evaluation of pharmaceuticals was published on 17 December 2012 (CHMP/ICH/752211/2012). The document should be read in conjunction with the photosafety testing section of ICH M3 (R2). It applies to new active substances and excipients for systemic administration, clinical formulations for topical application, dermal patches, ocular products and photodynamic therapy products.

Annexes to the CHMP/ICH and CVMP/VICH impurities guidance documents will come into effect in March 2013 (CPMP/QWP/450/03-Rev.1, EMEA/CVMP/511/03-Rev.1). They provide details on specifications for class 1 and class 2 residual solvents in active substances and specifications for finished products when organic solvents have been used in their manufacture.

Non-clinical development guidance

A draft joint CHMP/CVMP guideline on toxicological exposure limits and risk identification in the manufacture of different medicinal products in shared facilities was released for consultation until 30 June 2013 (EMA/CHMP/CVMP/SWP/169430/2012). The document addresses the issues surrounding the potential for cross-contamination when different active substances or finished products are produced in shared facilities. The document applies to all human and veterinary medicinal products, including investigational medicinal products, and active substances.

A draft notice on the planned changes to ICH guideline S1 on rodent carcinogenicity testing was published for public consultation until 1 April 2013 (EMA/CHMP/ICH/752486/2012). The document sets out a revised framework for assessing carcinogenicity, which would include conditions under which 2-year rodent carcinogenicity studies might be waived.

Pharmacokinetics guidance

A revised guideline on the investigation of drug interactions came into effect on 1 January 2013 (CPMP/EWP/560/95/Rev. 1 Corr.*). It provides recommendations on how to evaluate the potential for drug-food and drug-drug interactions and how to translate the findings in the product information. The document replaces guideline CPMP/EWP/560/95.

The 'Questions and answers' document on pharmacokinetics was updated to include a section on the number of subjects in a two-stage design bioequivalence study and a section on incurred sample reanalysis. Incurred sample reanalysis was introduced with the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) and is applied to assess the reliability of bioanalytical methods used in pre-clinical toxicokinetic studies and for a variety of clinical pharmacology studies (EMA/618604/2008 Rev. 7).

A draft guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms was released for consultation until 15 September 2013 (EMA/CPMP/EWP/280/96 Corr1). It sets out the studies to investigate the efficacy, safety, biopharmaceutical and pharmacokinetic properties of modified release and transdermal dosage forms.

Clinical development guidance

A revised guideline on the evaluation of anticancer medicinal products in man will come into effect on 1 July 2013 (EMA/CHMP/205/95).The finalised document includes revisions on the use of biomarkers during development, combination therapy studies and the choice of endpoints in confirmatory trials.

A draft guideline on the clinical investigation of products in the treatment of lipid disorders was released on 14 December 2012 (EMA/CHMP/718840/2012). The sections on the endpoints, long term safety, including morbidity/mortality data and imaging surrogate markers have been revised.

A draft guideline on the clinical development of products in Duchenne and Becker muscular dystrophy was published for consultation until 31 August 2013 (EMA/CHMP/236981/2011). The document discusses issues relating to the small number of patients in these conditions and its impact on e.g. study design, choice of efficacy and safety endpoints and definition of surrogate outcome measures.

A draft guideline on systemic lupus erythematosus was released for consultation until 4 September 2013 (EMA/CHMP/51230/2013). It sets out the clinical requirements for the development of products for systemic lupus erythematosus in adults and children, as well as cutaneous lupus and lupus nephritis forms.

A reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product was adopted on 21 February 2013. It outlines the principles for generating of quality, non-clinical and clinical data for these products. The document may also apply to other novel types of 'liposome-like' and vesicular products including those to be administered by routes other than intravenous administration (EMA/CHMP/806058/2009/Rev. 02).

Two draft standard paediatric investigation plans (PIPs) for acute myeloid leukaemia and rhabdomyosarcoma were released for consultation until 5 May 2013 (Link). Standard PIPs highlight requirements in selected indications and aim to support companies preparing PIPs. Further information and guidance on PIPs is available under Link.

Biologics and advanced therapies guidance

Four guidelines relating to the non-clinical and clinical development of biosimilars have been released :

- Recombinant human follicle stimulating hormone (EMA/CHMP/BMWP/671292/2010), coming into effect on 1 September 2013.
- Interferon beta (EMA/CHMP/BMWP/652000/2010), coming into effect on 1 September 2013.
- Insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 1), which presents the current views on the non-clinical and clinical requirements for the demonstration of comparability of two recombinant insulin-containing medicinal products. The draft is released for comments until 1 June 2013.
- Low-molecular-weight heparins (EMEA/CHMP/BMWP/118264/2007 Rev. 1), which details the need for clinical trials in the comparability programme due to the high heterogeneity of these products, the uncertainties on the structure-effect relationship and pharmacodynamic efficacy markers. The draft is released for comments until 31 July 2013.

A guideline on risk-based approach development for advanced therapies (gene, cell therapy and tissue engineering products) came into effect on 12 February 2013 (EMA/CAT/CPWP/686637/2011). The risk-based approach is a specific development strategy for advanced therapies which aims to determine the extent of quality, non-clinical and clinical MAA data. This strategy is optional and if it is selected by sponsors it should start early during development and evolve as the risk profile of the product is further defined. The risk-based approach is distinct from the concepts of risk management systems, environmental risk assessment and the MAA benefit/risk assessment.

A reflection paper on the classification of advanced-therapy medicinal products was announced on 17 December 2012 (EMA/CAT/600280/2010). It provides details on the scientific grounds applied for such reviews and outlines the latest issues in this evolving field.

Guidance on pharmacovigilance (Human medicines)

To support the implementation of new EU pharmacovigilance legislation which entered into force in July 2012, a series of guidelines have been developed to replace Volume 9A of the Rules Governing Medicinal Products in the EU. This guidance on good pharmacovigilance practices (GVP) is organised into Modules. Modules III-Pharmacovigilance inspections (EMA/119871/2012), IV-Pharmacovigilance audits (EMA/228028/2012) and XV-Safety communication (EMA/118465/2012) are now published in their final versions, together with the updated GVP Annex on definitions (EMA/876333/2011 Rev. 1*.).

An ICH guideline [E2C (R2)] on periodic benefit-risk evaluation report (PBRER) came into effect in January 2013 (EMA/CHMP/ICH/544553/1998). The PBRER is intended to be a common standard for the periodic reporting of benefit-risk evaluation among the ICH regions. The document defines the recommended format and content of a PBRER and provides an outline of points to consider in its preparation and submission.

A revised list of the 'European Union reference dates' (EURD) and frequency of submission of periodic safety update reports was released on 21 December 2012. It consists of a comprehensive list of active substances and combinations of active substances sorted in alphabetical order, for which Periodic Safety Update Reports (PSURs) should be submitted. The list has been compiled in order to facilitate the harmonisation of data lock points and frequency of submission of PSURs. The list will become legally binding on 1 April 2013, Further information on transitional arrangements applying to PSURs and EURD are available under Link.

Updated reporting requirements of individual case safety reports applicable to marketing-authorisation holders during the interim period were released on 8 January 2013 (EMA/321386/2012 Rev. 4).

A document on distant/virtual pharmacovigilance inspections of marketing-authorisation

holders during a crisis situation was released on 18 February 2013 (EMA/INS/119905/2012). The need to perform pharmacovigilance inspections during crisis situations (e.g. pandemics, natural disasters, transport restrictions) has been identified as an important issue. The document sets out the specificities of such inspections and circumstances where these could replace on-site inspections.

Guidance for veterinary medicines

Three VICH guidelines will come into effect in Q1 2014 on:

- the statistical evaluation of stability data (VICH GL5; EMA/CVMP/VICH/858875/2011)
- the harmonization of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use (VICH GL50; EMA/CVMP/VICH/582610/2009)
- the testing of biologicals for the detection of Mycoplasma contamination (VICH GL34; EMA/CVMP/VICH/463/2002)
- the electronic standards to construct a single electronic message for the transfer of data of animal adverse events (VICH GL35;EMA/CVMP/VICH/123940/2006).

A draft VICH (GL23) guideline on genotoxicity testing to evaluate the safety of residues of veterinary drugs in human food was released for public consultation until 31 March 2013 (CVMP/SWP/398880/2012). It sets out recommendations for a standard battery of genotoxicity tests and suggests modifications to the choice of tests or to the protocols which may be needed for certain drugs such as antimicrobials.

A draft reflection paper on the use of pleuromutilins in food-producing animals, the development of resistance and its impact on human and animal health was published for public comments until 30 June 2013 (EMA/CVMP/SAGAM/119489/2012).

Recommendations on the causality assessment for adverse events to veterinary medicinal products were posted for consultation until 31 May 2013 (EMA/CVMP/PhVWP/552/2003 – Rev.1). The document replaces the guideline EMEA/CVMP/552/03 and includes additional information on the causality assessment of adverse events classified as off-label.

Regulatory and procedural guidance

The eSubmission web client for electronic submissions was released in January 2013. It is a free, web-based tool which complements the existing Gateway by offering applicants the possibility to submit eCTD applications securely over the internet directly to the Agency (Human medicines dossier only at present). Further information is available under Link.

A draft paper on good-clinical-practice (GCP) compliance for trial master files (paper and/or electronic) for the management, audit and inspection of clinical trials was released for consultation until 30 April 2013 (Link). It summarises the requirements for trial master files and provides recommendations and advice on issues such as archiving and retention times.

The European Commission published in 2012 a guideline on results-related information on clinical trials (2012/C 302/03) and a related technical guidance in January 2013 (Link) .These documents provide details on the posting in EudraCT and the publication in the EU clinical trial register of clinical trials results summaries directly by sponsors. The system will be piloted in Q2 2013 and is targeted to be in production at the end of 2013. For further information contact EudraCT@ema.europa.eu.

Pre- and post-authorisation regulatory information for applicants of centralised dossiers was released on:

- Type IA, IB, II, grouped, work-sharing variations and line-extensions. Updates related to categorization, grouping, dossier requirements, product information changes and fees (EMEA-H-19984/03 Rev 27)
- Orphan policy:
  - Assessment of similarity in initial dossiers (EMA/339324/2007)
  - Post-authorisation dossiers and market exclusivity, line-extensions for orphan and non-orphan indications (EMEA-H-19984/03 Rev 27);
  - Generic/hybrid dossiers with orphan product used as reference and related similarity

issues (EMEA/CHMP/225411/2006).

— Orphan fees (Link).

- Adjusted EMA fees applicable from 1 April 2013 (Link)
- Simplified/reduced number of dossiers required for EMA/NCA/Committees for initial and post-authorisation dossier submissions (Link)

Registered SMEs

Currently, 1,059 companies have SME status assigned by the Agency. Their names and profiles are published in the Agency's public SME Register.

If you would like to have your company details included in the SME Register, you must first apply for SME status at the Agency. See the How to apply section of the SME Office pages on the Agency's website for information on how to do this.

The Innovation Office of the Medical Products Agency in Sweden

The Swedish Medical Products Agency has recently launched an Innovation Office to support life sciences innovators in academia and industry, including small businesses.

For further information on their activities, and how to subscribe to their newsletter, please refer to:

http://www.mpa.se/innovationenq

About the SME Office

The SME Office was set up within the European Medicines Agency to address the particular needs of smaller companies.

The Office has dedicated personnel who can help SMEs by:

- responding to practical or procedural enquiries;
- monitoring applications;
- organising workshops and training sessions.

Need more information?

Visit the European Medicines Agency website:

http://www.ema.europa.eu

In particular, these sections may interest you:

SME Office
Pre-authorisation (human medicines)
Pre-authorisation (veterinary medicines)

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