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:

Pharmaceutical development guidance

A revised guideline on the investigation of bioequivalence was published on 29 January 2010 (CPMP/EWP/QWP/1401/98 Rev. 1). The document was prepared following an extensive public consultation and represents a major regulatory guideline for companies planning bioequivalence studies. It also includes recommendations on BCS (Biopharmaceutics Classification System)-based biowaiver approach which are intended to reduce in vivo bioequivalence studies with in vitro data. This strategy is restricted to highly soluble drug substances with known human absorption and that are not considered to have a narrow therapeutic index. The revised guidance will replace the 'Note for guidance on the investigation of bioavailability and bioequivalence' (CPMP/QWP/EWP/1401/98) and the related questions in the 'Questions and answers' document (CHMP/EWP/40326/06). The guideline will come into effect on 1 August 2010.

A draft guideline on the requirements for quality documentation concerning biological investigational medicinal products (IMP) in clinical trials was published on 11 February 2010 (EMA/CHMP/BWP/534898/2008). Available guidelines on the quality of biological/biotechnological medicinal products mainly address quality requirements for marketing authorisation applications which may not be fully applicable in the context of a clinical trial application. Whilst the marketing authorisation dossier aims to ensure a consistent, state-of-the-art quality of a product for widespread use in patients, the information to be provided for an IMP should mainly focus on quality attributes related to safety aspects. The draft guidance addresses the quality requirements of an IMP for a given clinical trial and does not provide guidance on a company's overall development strategy for a medicinal product. Companies wishing to discuss the quality documentation to support a marketing authorisation application are advised to seek Scientific Advice at European or National level. The guidance is released for consultation until 31 August 2010.

A draft guideline on 'Real time release testing' (formerly known as 'Parametric Release') for human medicines was released on 3 March 2010 (EMA/CHMP/QWP/811210/2009 Rev 1). Compliance with release specifications can be demonstrated by performing a complete set of tests on finished products according to the approved specifications. Under certain conditions, an alternative strategy to routine testing is possible. So far this concept has been only applied to sterility testing of terminally sterilised products ('parametric release'). Recent ICH guidelines have made it possible to apply a similar release strategy to tests other then sterility. This approach has been called Real Time Release testing. The guideline replaces the previous guideline on parametric release and does not introduce new requirements; the parametric release part of the previous guideline is unchanged. It is released for consultation until is 31 August 2010.

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The following Annexes to ICH Quality topics relating to the official pharmacopoeial texts (Ph.Eur, JP, USP) recommend that the following tests can be used interchangeably in the ICH regions:

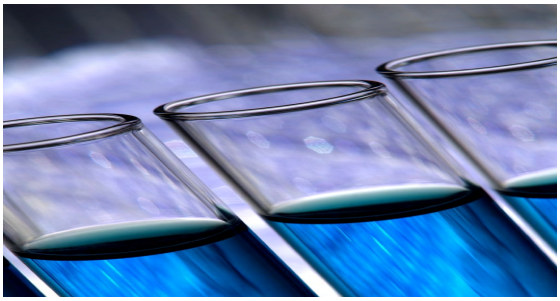
- Q4B Annex 7 Dissolution test (EMEA/CHMP/ICH/645469/2008) (applicable as of May 2010)
- Q4B Annex 9 Tablet Friability (EMEA/CHMP/ICH/379801/2009) (applicable as of May 2010)
- Q4B Annex 10 Polyacrylamide Gel Electrophoresis (EMEA/CHMP/ICH/381133/2009) (applicable as of May 2010)
- Q4B Annex 11 Capillary Electrophoresis (EMEA/CHMP/ICH/730028/2009) (Released for consultation)
- Q4B Annex 12 Analytical Sieving General Chapter (EMEA/CHMP/ICH/730808/2009) (Released for consultation)

The following 'Questions and Answers' documents were published on:

- 'ICH Topic Q8, Q9 and Q10/Note for Guidance on Pharmaceutical Development Quality Risk Management Pharmaceutical Quality System' released on 18 December 2009 (EMEA/CHMP/ICH/265145/2009). The 'Questions and Answers' document was developed to facilitate the implementation of existing guidelines in a consistent way across the three ICH regions.
- Annex 1 of the GMP Guide' was updated in January 2010 (Link). Specific questions on the interpretation of GMP requirements should generally be addressed by the Qualified Person directly to the relevant supervisory authority of the Member State in which the manufacturing authorisation holder is located. The EMA regularly updates the 'Questions and answers' document following discussion with the EMA specialised groups dealing with inspections matters.
- The 'Questions and Answers' document developed by the Joint CHMP/CVMP Quality Working Party (QWP) providing recommendations on matters relating to the quality of human or veterinary medicinal products. It was updated to include information on stability issues of pharmaceutical bulk products for use in manufacture of finished products (Link).

Preclinical and clinical guidance

A draft guideline on validation of bioanalytical methods was released on 8 December 2009 (EMEA/CHMP/EWP/192217/2009). It provides recommendations for the validation of bioanalytical methods used for pharmacokinetic sample analysis. It also addresses specific aspects of the bioanalytical method itself e.g. the actual analysis of samples from toxicokinetic studies and clinical trials and when partial or cross validation may represent an appropriate alternative approach to the complete validation of an analytical method. It is released for consultation until 31 May 2010.



A revised ICH guidance 'Topic S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals' was released on 18 December 2009 (CHMP/ICH/302/95). Scientific advances and experience gained since the publication of the original guidance called for the development of an harmonised addendum on species selection, study design, immunogenicity, reproductive and developmental toxicity and assessment of carcinogenic potential.

An ICH guidance 'Topic S9 Non-clinical Evaluation for Anticancer Pharmaceuticals' was released on 18 December 2009 (EMEA/CHMP/ICH/646107/2008). It provides advice on the design of non-clinical studies program to support the development of oncology pharmaceuticals for the treatment of patients with advanced disease and limited therapeutic options.

An updated 'Questions and answers on the CHMP guideline on limits of genotoxic impurities' was published on 14 January 2010 (EMA/CHMP/SWP/431994/2007/Revision 2).

Regulatory advice

Presubmission procedural advice on the centralised procedure was updated on 5 March to include information on eligibility to the centralised procedure, rapporteurships' appointment and accelerated assessment (Link). The SME office emphasises the usefulness of early pre-submission dialogue (i.e. 'SME Briefing meeting') and encourages future SMEs applicants to engage in regulatory presubmission dialogue well ahead of the current marketing authorisation application presubmission meeting timelines (i.e. 7 months before submission) to discuss procedural, regulatory, legal aspects of their future marketing authorisation application.

The rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency have been revised (EMA/MB/170391/2009/Rev.4) and an updated explanatory note on fees payable to the EMA (EMA/649350/2009) was released on 15 December 2009. The documents detail the fees applicable to EMA procedures as of 1 January 2010. SMEs are reminded to apply for financial incentives in line with the following guidance (Link).

An updated 'Questions and Answers document on ICH Topic M 2/Common Technical Document for the Registration of Pharmaceuticals for Human Use' (Link) was published on 18 December 2009. It includes clarifications on the XML structure and attributes used in Modules 2 and 3 of the Common Technical Document.

Guidance on the expression of strength in the name of centrally authorised human medicinal products was announced on 12 January 2010 (EMA/707229/2009). The recommendations apply only to the determination of the strength in the name of medicinal products and do not automatically affect other regulatory decisions (e.g. policies regarding the system of issuing authorisation numbers, fees calculation, classification of extension versus variation applications). The guidance will apply to new marketing authorisation applications in the centralised procedure as of 1 March 2010 and will not apply retrospectively to authorised medicinal products.

A guidance document on Regulation (EC) No 1234/2008 ('The 'Variation Regulation') was released on 20 January 2010 (EMA/40404/2010). It addresses a number of questions which Marketing Authorisation Holders (MAHs) may have on post-authorisation procedures.

Paediatric medicines

The guidance for applicants on 'Paediatric investigation plans (PIPs), waivers and modifications' was updated to include information on a pilot initiative aimed at SMEs. As of 2010, SMEs developing medicines for children will be able to request presubmission meetings, before the application for PIP and/or Waiver is actually submitted. Further information on this initiative aiming to assist SMEs is available in the guidance document (Link). The document was also revised to include updated regulatory, procedural and administrative information, and revised templates as follows:

- Template for PIP/waiver letter of intent
- Template for PIP applications or request for waiver
- Form for non-clinical and clinical studies proposed in a PIP application
- Template to change applicant name or details
- Submission deadlines for 2012 and 2013 for PIP and answers to Request for Modification
- Submission deadlines for 2012 and 2013 for submitting request for a modification to an agreed PIP
- Submission deadlines for 2012 and 2013 for submitting request for compliance check

Orphan drugs

The Orphan drugs Section has released a series of guidance documents to help sponsors planning to submit an application for orphan drug designation (EMA/710916/2009/Rev 4; EMA/710915/2009/Rev 5; EMA/710917/2009/Rev 5; EMA/41277/2007 Rev. 3). It includes practical advice on pre-submission meetings, preparation of the orphan drug designation dossiers and procedural aspects. As an additional measure to ease the administrative burden on applicants, only electronic submissions of applications for orphan designation will now be accepted for review (EMA/22383/2010). Sponsors of orphan drugs also have the option of submitting a single annual report to the Agency and the US Food and Drug Administration for products designated in both regions (EMA/121846/2010).

Advanced therapies

A 'Questions and Answers' document on gene therapy was published on 13 January 2010 (EMA/CHMP/GTWP/212377/2008). It provides a harmonized position on issues related to the development of gene therapy medicinal products that can be subject to different interpretation.

A concept paper on the revision of the note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products was published on 13 January 2010 (EMA/CHMP/GTWP/BWP/234523/2009). It sets out the multidisciplinary revisions of the gene therapy guidance (CPMP/BWP/3088/99) that came into effect in 2001. The future guidance will address the significant progress and experience gained from science and technology advances, clinical experience, and regulatory considerations.

A concept paper on the development of a guideline on the 'risk-based approach' for advanced therapies was released on 26 January 2010 (EMA/CHMP/CPWP/708420/2009). The revision of Directive 2001/83/EC (Link) introduced a new concept of 'risk-based approach' for 'advanced therapy medicinal products' (ATMP). It is based on the identification during the development program of risk factors inherent to the nature of the ATMP and associated e.g. with the biological characteristics and origin of the cells, the manufacturing process, the biological characteristics of used vectors and the therapeutic use of the product. These together with the appropriate non-clinical and clinical testing should be part of the overall strategy to minimise the risks of the ATMP. The risk-based approach would need to be detailed in Module 2 of any future Marketing Authorisation Application. The concept paper sets out the background, rationale and content of the future guideline.

SMEs developing advanced therapies are particularly invited to provide comments on the above documents.

Veterinary medicines

A series of guidance documents on residue chemistry data for veterinary drugs used in food-producing animals were released on 22 December 2009. They were prepared after consideration of the current requirements in the European Union, Japan, United States, Australia, New Zealand and Canada to facilitate the mutual acceptance of residue chemistry data for veterinary drugs used in food-producing animals. The documents released for consultation until 20 May 2010 are the following:

- A VICH guidance 'Topic GL49 Guideline on validation of analytical methods used in residue depletion studies' (EMEA/CVMP/VICH/463202/2009). The document intends to harmonise across ICH regions the validation requirements for the methodology used during residue studies submitted to the regulatory agencies in support of the maximum residue limits (MRLs) and withdrawal periods.
- A VICH guidance 'Topic GL48 Guideline on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods' (EMEA/CVMP/VICH/463199/2009). It provides study design recommendations which will facilitate the universal acceptance of the generated residue depletion data to fulfil this requirement.
- A VICH guidance 'Topic GL47 Guideline on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: comparative metabolism studies in laboratory animals' (EMEA/CVMP/VICH/463104/2009). It recommends internationally harmonized procedures for comparative metabolism studies aiming to determine if laboratory animals used for toxicological testing have been exposed to the metabolites that humans will be exposed to as residues in products of food animal origin.
- A VICH guidance 'Topic GL46 Guideline on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues' (EMEA/CVMP/VICH/463072/2009). The objective of this guidance is to provide recommendations for internationally harmonized test procedures to study the quantity and nature of residues of veterinary drugs in food-producing animals.

News from the European Commission

A report ('Study on the competitiveness of the European biotechnology industry') on the financing of biopharmaceutical product development in Europe was published by the European Commission (ENTR/06/054). It was prepared with the help of the European Commission's Entrepreneurship and Innovation Programme (EIP) under the Competitiveness and Innovation Framework Programme (CIP). It reviews the access to finance for biopharmaceutical companies in Europe to analyse these challenges and to formulate evidence-based policy recommendations that can support the competitiveness and innovative capacity of the European biopharmaceutical sector.

The European Commission launched on 18 November 2009 a public consultation on 'EudraLex-The Rules Governing Medicinal Products in the European Union-Volume 4-EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use-*Part I-chapter 1* of the Good Manufacturing Practices laying down the guidelines on Quality Management System' (Link). The proposed revisions include changes to integrate the principles of "Pharmaceutical Quality System" described in the ICH Q10 tripartite guideline. The following sections have been added to Chapter 1:

- Quality Management System
- Process Performance and Product Quality Monitoring System and Product Quality Review
- Management of Outsourced Activities and Purchased Materials
- Management of Review on the Quality Management System
- Monitoring of Internal and External Factors Impacting the Quality Management System
- Outcomes of Management Review and Monitoring

The document is released for consultation until 31 May 2010.

Meetings

The following meetings which might be of interest to SMEs have been announced:

- The European Medicines Agency's workshop on Nanomedicines on 26-27 April 2010
- 10 years of the Orphan Regulation in Europe on 3-4 May 2010
- The European Medicines Agency's workshop on Stem cell-based therapies on 10 May 2010

Further information and details about registration is available here.

Please also note that a Training Workshop on "Regulatory considerations in initiating clinical trials" organised by the SME Office will take place on 28 May 2010. Further information and details about registration is available here.

SME companies registered with the Agency

407 companies currently have SME status assigned by the Agency. The list of companies is published on the Agency's 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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