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:



## Non-clinical and clinical guidance

A draft guideline on the clinical investigation of medicinal products in the treatment of depression was released on 11 October 2011 (EMA/CHMP/185423/2010, Rev 2). The guideline was reviewed based on experience with recent clinical development programs, marketing authorisations, scientific advice procedures, new results in basic science and guidelines reflecting current medical practice. The need for placebo control and active control is outlined, issues regarding special populations like children and adolescents, young adults and the elderly have also been addressed. As DSM IV and ICD-10 are currently under revision and there is a trend to implement more dimensional aspects to defining depression, this might have consequences for the definitions included in the current document. The deadline for comments is 31 March 2012.

*'Appendix IV of the guideline on the investigation on bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1): Presentation of biopharmaceutical and bioanalytical data in module 2.7.1'* was published in November 2011 and will come into effect in June 2012 (EMA/CHMP/600958/2010/Corr.*). The objective of CTD Module 2.7.1 is to summarise information relating to biopharmaceutical studies and associated analytical methods. The *'Appendix'* contains a set of template tables to assist applicants in the preparation of Module 2.7.1 and provides guidance on how the data should be presented. It is intended for generic applications and may also be used for other applications such as hybrid applications, fixed combinations, variations and extensions dossiers where appropriate.

A draft guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH) was made public on 24 November 2011 (EMA/CHMP/BMWP/671292/2010). The non-clinical section addresses the pharmaco-toxicological requirements. The clinical section provides guidance on the pharmacodynamic, pharmacokinetic, efficacy and safety studies needed for the demonstration of comparability of two FSH-containing medicinal products as well as the required risk management measures. The criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are also discussed. The deadline for comments is 31 May 2011.

## Non-clinical and clinical guidance (continued)

Three scientific advice/qualification opinions on novel methodologies and biomarkers relating to drug development in Alzheimer's disease were released in December 2011:

1. Use of low hippocampus volume (atrophy) by MRI in clinical trials for regulatory purpose in pre-dementia stage of Alzheimer's disease (EMA/CHMP/SAWP/809208/2011; *Finalised*).
2. Use of cerebrospinal fluid amyloid beta 1-42 and t-tau signature and/or positron emission tomography-amyloid imaging (positive/negative) as biomarkers for enrichment in regulatory clinical trials in mild/moderate Alzheimer's disease (EMA/CHMP/SAWP/893622/2011; under *consultation* until December 2011).
3. Positron emission tomograpy amyloid imaging (positive/negative) as a biomarker for enrichment in predementia Alzheimer's disease clinical trials (EMA/CHMP/SAWP/893622/2011; under *consultation* until December 2011).

## Pharmacovigilance

The new pharmacovigilance legislation package (Regulation 1235/2010 and Directive 2010/84/EU) was adopted in December 2010. One of the implementing measures for applicants and holders of EU marketing authorizations is the supply of product information to the EMA on medicinal products for human use, authorised or registered in the EU using an electronic format provided by the Agency. Marketing-authorisation holders will also be responsible for updating this information. Detailed information on the requirements is available under Link1 and Link2. A training program is currently being developed by the Agency. Further information will be announced on the EMA and EudraVigilance websites.

A draft *'ICH guideline E2B (R3): Electronic transmission of individual case safety reports (ICSRs) - implementation guide - data elements and message specification: Step 3'* (EMA/CHMP/ICH/166783/2005) and its *'Appendix'* (EMA/CHMP/ICH/818331/2011) were released on 25 October 2011. The guideline is a technical guide intended to support the implementation of software tools for creating, editing, sending and receiving electronic ICSR messages. The guide should be consulted by system developers, IT professionals and system users who need to understand the requirements for constructing and using valid electronic messages to transmit ICSRs. Its *'Appendix'* is intended to assist in implementing systems for conversion back and forth between the previous standard i.e. E2B(R2) and the new one i.e. E2B(R3). The evolution of the standard from E2B(R2) to E2B(R3) has the consequence that ICSRs cannot be perfectly converted from one version to the other. The documents are released for consultation until March 2012.

## Veterinary guidance

A VICH guidance *'GL18(R): Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients (Revision)'* was adopted on 26 September 2011 (EMA/CVMP/VICH/502/99-Rev.1). It recommends acceptable amounts for residual solvents in pharmaceuticals for the safety of the target animal as well as for the safety of residues in products derived from treated food producing animals. The guidance applies to residual solvents in active substances, excipients and in veterinary medicinal products. It does not apply to new active substances, excipients or veterinary medicinal products used during the clinical research stages of development nor does it apply to existing marketed veterinary medicinal products. It will come into effect in July 2012.

## Veterinary guidance (continued)

A guideline on the safety and efficacy of fish vaccines was published on 29 November 2011 (EMA/CVMP/IWP/314550/2010). It provides information on the design and conduct of studies to support the safety and efficacy of immunological veterinary medicinal products (IVMPs) in finfish. It also includes considerations for both laboratory scale size and field trials to ensure that these are representative of the safety and efficacy of the vaccine when administered in accordance with its intended use (e.g. type of fish to be used; water conditions, method of administration, use of control groups). It will come into effect in May 2012.

A draft guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) was released on 29 November 2011 (EMA/CVMP/IWP/594618/2010). It outlines the data requirements in relation to marketing authorization applications for combined vaccines and applications where an association between two or more different IVMPs is claimed by the applicant. It revises and compiles into a single document the existing *'guideline on requirements for concurrent administration of IVMPs'* and the *'guidance on combined veterinary vaccines'*. It is released for consultation until 30 April 2012.

## New legislative proposals and regulatory impact assessments

The revised draft directives and regulations setting out the new requirements for information on prescription-only medicines were published in October 2011 (Link). The new legislative proposals set out a framework whereby marketing authorization holders will have to provide good quality and objective information on their prescription-only medicines to the general public. The key elements of the amended proposals are:

1. Only certain information on prescription-only medicines would be allowed e.g. from the label and package leaflets, the pre-clinical tests and the clinical trials; pricing information and instructions for proper use.

2. Only certain channels of communication will be allowed for providing information e.g. via officially registered internet websites or through printed information, if this had been specifically requested by members of the public.

3. All information would have to be of the highest quality, objective, unbiased and easily understandable.

4. Information which has not been approved before would need to be verified by competent authorities prior to its dissemination.

The revised proposals will be discussed by the European Parliament and the Council of Ministers in 2012.

Two concepts papers on the implementation of the EC Directive on falsified medicines (Directive 2011/62/EU) have been released in November 2011. The documents have been published with a view to preparing the impact assessments and the delegated acts required by the Directive. SMEs and their stakeholders are particularly invited to comment on these documents.

1. *'Detailed rules for a unique identifier for medicinal products for human use, and its verification'* (Link). The topics for consultation relate to the requirements introduced by the directive for obligatory safety features to allow verification of the authenticity of medicinal products ('unique identifier'): characteristics and technical specifications of the unique identifier; modalities for verifying the safety features; provisions on the establishment, management and accessibility of the repositories system; lists containing the medicinal products or product categories which, in the case of prescription medicines shall not bear the safety features, and in the case of non-prescription medicines shall bear the safety features. The deadline for comments is 27 April 2012.

## New legislative proposals and regulatory impact assessments (continued)

2. *Requirements for the assessment of the regulatory framework applicable to the manufacturing of active substances of medicinal products for human use'* (Link). The topics for consultation relate to the requirements introduced by the Directive for third countries' active substance manufacturers to ensure that the standards of good manufacturing practice (GMP) and control of the plant are equivalent to those in the EU: equivalence assessment of the rules for GMP, equivalence assessment of the regularity of inspections to verify compliance with GMP and the effectiveness of enforcement of GMP, regularity and rapidity of information provided by third countries relating to non-compliant producers of active substances. The deadline for comments is 23 March 2012.

## Regulatory and legal updates, e-CTD

The post-authorisation procedural advice for users of the centralised procedure was revised in September 2011 to include information on transfers of marketing authorizations (EMEA-H-19984/03 Rev 20).

The European Commission has issued a revised note on how it handles requests from pharmaceutical companies for duplicate marketing authorisations. The revised note was updated to provide clarifications on the application of Article 82(1) of the Regulation 726/2004 (Link).

A new version of the validation criteria for electronic applications for human medicines came into effect on 1 September. The EMA is now applying new electronic common technical document (eCTD) validation criteria (version 3.1) upon technical validation of all eCTD sequences received. Further information is available under Link.

## Meetings

A conference on diabetes and obesity has been announced: *'Disability - A World-Wide Challenge Towards a global initiative on gene-environment interactions in diabetes/obesity in specific populations'.* The meeting which is organized by the European Commission's DG Research will take place on 9-10 February 2012 in Brussels. It will present the state of play in the diabetes and obesity fields and explore opportunities for international cooperation and partnerships. Further information is available here.

## SME companies registered with the Agency

675 companies currently have SME status assigned by the Agency. The companies are published in the Agency's public SME registry at: http://fmapps.emea.europa.eu/SME/

## 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 or queries on this news bulletin can be forwarded to the SME Office:

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