EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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

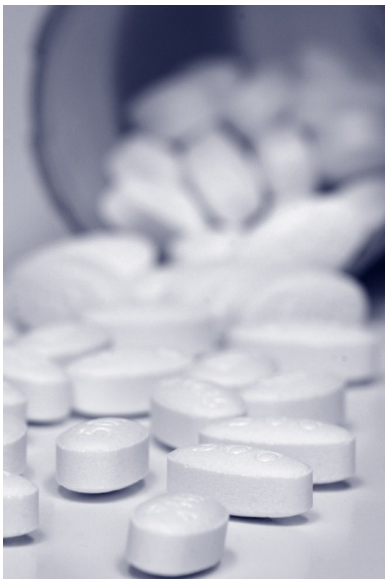
A reflection paper on the considerations given to designation of a single stereoisomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance was adopted on 21 November 2012 (EMA/651649/2010). It aims at harmonising the classification to enable a consistent interpretation across European authorisation systems with a view to *e.g.* clarifying scientific requirements of development programmes and the access to the centralised procedure. Applicants will have to provide evidence to justify their claims of *new active substance* status in their marketing authorisation submission in light of the guidance.

A draft guideline on the use of bovine serum in the manufacture of human biological medicinal products was released for consultation until 31 December 2012 (EMA/CHMP/BWP/457920/2012 rev. 1). It outlines the general principles for the control of the quality and safety of bovine serum used during the manufacture of human biological medicinal products. The revisions include changes to the testing requirements for bovine viral diarrhoea virus (BVDV) and anti-BVDV antibodies, which have been revised in accordance with the requirements applied for the production of immunological veterinary medicinal products (EMEA/CVMP/743/00-rev 2.).

A draft guideline on the quality of transdermal patches was released for consultation until 15 March 2013 (EMA/CHMP/QWP/911254/2011). Together with the new guideline on oral modified release products (see below), it replaces the guidance on *'Modified Release products: A: Oral dosage Forms B: Transdermal Dosage Forms. Part I (Quality)'.* The document sets out the quality requirements for the development of a transdermal patch for all new marketing authorisation applications and subsequent variations as well as providing information for generic applications. Cutaneous patches i.e. not intended to be systemically absorbed, are outside the scope of the guideline.

A draft guideline on the quality of oral modified-release products was published for consultation until 15 March 2013 (EMA/492713/2012). The document covers delayed release oral dosage forms with properties of gastro-resistance and prolonged release. Many principles discussed in the document with respect to prolonged release oral dosage forms will be relevant to other modified release dosage forms intended for oral administration or via other routes.

Clinical development guidance



A guideline on the clinical development of medicinal products for schizophrenia, including depot preparations (EMA/CHMP/40072/2010 Rev. 1) will come into effect on 1 April 2013. The document was revised to take into account the changes in clinical study outcomes performed in patients with schizophrenia in the last decades (e.g. higher placebo response, stability of clinical response) and reviews study designs in terms of use of placebo, study duration, and patient population. The guideline was developed during a transitional period in which the DSM IV classification and diagnostic criteria for schizophrenia (and other psychotic conditions) is being revised in the preparation for DSM V. This guideline does not address psychotic conditions other than schizophrenia.

A draft guideline on the clinical investigation of products for the treatment of Multiple Sclerosis was released for consultation until 9 April 2013 (EMA/CHMP/771815/2011, Rev 2). Its main focus is on products that modify the natural course of the disease which require long term superiority trials with relapse rate and disability as the most important endpoints. It is proposed that products affecting the immune system should first be evaluated in a comparative superiority study in patients with insufficient response to first line treatment. If the safety profile is deemed acceptable, studies may be extended to a broader population. Details are also provided on the generation of data in children (specific children studies, incorporation in adults studies or extrapolation).

A draft guideline on the clinical investigation of medicinal products for the treatment of acute heart failure has been released for consultation until 15 April 2013 (CHMP/EWP/2986/03 Rev. 1). The document is a revised version of the addendum of the guidance on chronic heart failure (CHMP/EWP/235/95, rev. 1). It was updated in relation to the factors in particular patient characteristics that impact on the outcome of acute heart failure trials and their evaluation. It focuses only on *pharmacological* interventions intended for left ventricular dysfunction with or without concomitant right ventricular dysfunction.

A draft guideline on hepatitis-B immunoglobulins was released for consultation until 31 May 2013 (EMA/CHMP/BPWP/585257/2009). It describes the clinical requirements for marketing authorisation application for new hepatitis B immunoglobulins and authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures). The document covers plasma-derived hepatitis B immunoglobulins defined by the relevant European Pharmacopoeia monographs and does not relate to fragmented or chemically modified products.

A draft guideline on human normal immunoglobulin for subcutaneous and/or intramuscular administration was released for consultation until 3 June 2013 (EMA/CHMP/BPWP/410415/2011 Rev 1). It revises and replaces guidance 'CPMP/BPWG/283/00' to align with the guidance relating to intravenous immunoglobulins and includes information on marketing authorisation requirements such as biological data, pharmacokinetics, clinical trials and patient follow-up.

A paediatric addendum to the guideline on the clinical investigation of medicinal products in the treatment of lipid disorders will come into effect on 20 March 2013 (EMA/CHMP/494506/2012). The addendum highlights specific paediatric issues for lipid disorders and differences from adult patients.

Guidance for veterinary medicines

An updated 'Questions and answers' on the implementation of the CVMP guideline on environmental impact assessment in support of the VICH guidelines GL6 (phase I) and GL38 (phase II) was released on 20 September 2012 (EMEA/CVMP/ERA/172074/2008-Rev.4).

An updated guideline on the approach to establish a pharmacological acceptable daily intake (ADI) will come into effect on 1 June 2012 (EMA/CVMP/SWP/355689/2006). It provides guidance on when to establish a pharmacological ADI and on pharmacodynamic endpoints.

A draft guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMP) was released for consultation until 15 January 2013 (EMA/CVMP/IWP/594618/2010). It provides guidance on the data requirements to support authorisation of combined vaccines and a claim for the use of two or more IVMPs used in association. It replaces the guidelines on concurrent administration of immunological veterinary medicinal products (EMEA/CVMP/550/02) and on requirements for combined veterinary vaccines (CVMP/IWP/52/97).

A draft guideline on non-steroidal anti-inflammatory drugs (NSAIDs) was released for consultation until 31 May 2013 (EMA/CVMP/EWP/1061/2001). It sets out recommendations for the design, conduct, and evaluation of preclinical and field studies submitted in support of an application to authorise a new non-steroidal anti-inflammatory product or to vary the indications of an already authorised one.

A draft guideline on the demonstration of palatability of veterinary medicinal products was released for consultation until 31 May 2013 (EMA/CVMP/EWP/206024/2011). It specifies the requirements for the design, conduct, and evaluation of *in vivo* palatability studies for all oral dosage forms of pharmaceutical veterinary medicinal products intended for individual or group animal treatment.

Guidance on Pharmacovigilance (Human medicines)

The following updated documents were released:

- Detailed guidance on the electronic submission of product information by marketing-authorisation holders to the European Medicines Agency in accordance with Article 57(2) (EMA/720203/2011).
- Questions and answers on the pharmacovigilance legislation (EMA/228816/2012–v.2) updated in relation to the pharmacovigilance system master file, post-authorisation studies, adverse drug reaction reporting and signal management.
- Reporting requirements for individual case safety reports applicable to marketing-authorisation holders during the interim period (EMA/321386/2012 Rev. 3).
- EU risk-management plan templates (EMA/718034/2012). The documents should be read and completed in vue with GVP module V. A modular approach has also been made available to allow for the reuse of modules across different regulatory documents. The templates will apply from 10 January 2013.

Information on reference Dates and frequency of PSUR submission (the 'EURD list') was released on 1 October 2012 (Link and explanatory note). The EURD list is a comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different marketing authorisations, together with the corresponding EU reference dates, frequencies for submission of PSURs and related data lock points. The EURD list aims to optimise the management of PSUR submission and single PSUR assessment within the EU.

Regulatory and procedural guidance

The following updated documents were released:

- Policy on the determination of the condition(s) for a paediatric investigation plan/waiver (EMA/272931/2011). The document sets out the implementation of a *pilot* phase of a regulatory policy for identifying an overarching condition when evaluating the paediatric development of a product in relation to the condition, the PIP indication and the therapeutic indications proposed by companies.
- Pre-submission procedural advice for users of the centralised procedure (updated in relation to definition of strength, fees and MAA presubmission meetings) (Link).
- Post-authorisation procedural advice for users of the centralised procedure (updated in relation to Type Ia, Ib variations, Type II variations, grouping of variations, renewals, transfers definition of strength, fees and MAA presubmission meetings) (Link).
- Transitional provisions for the implementation of variation Regulation (EC) No 1234/2008 (EMA/626908/2012).

Public consultations

A public consultation on a black symbol identifying 'medicines subject to additional monitoring' was released on 21 November 2012 (Link). The concept of additional monitoring was introduced with the latest pharmacovigilance legislation for medicines which would need an enhanced data collection. Such products will be identified with a black symbol in the product information and the package leaflet. The consultation period is open until 10 January 2013.

Meetings

The reports of the following meetings were posted:

- Workshop in ophthalmology (Link)
- Workshop on pharmacogenomics (Report; Link to presentations)
- Ethical considerations for paediatric trials (Link)
- Workshop on clinical-trial data and transparency (Link)

The following workshops have been announced:

- Regulatory workshop on medication errors at the European Medicines Agency, 28 February 2013- 1 March 2013 (Link)

SME companies registered with the Agency

1088 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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