EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

News bulletin for small and medium-sized enterprises

ISSUE 19 MARCH 2012

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 clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs (e.g. disease-modifying anti-rheumatic drugs, biologicals) for the treatment of rheumatoid arthritis (RA) was released on 20 December 2011 (CPMP/EWP/556/95 Rev. 2). This document is a revision of the 'Points to Consider' adopted in November 2003 and takes into account developments relating to study design and validated disease activity evaluation tools to assess clinical and structural outcomes. The scope of the guidance is on rheumatoid arthritis only. Separate guidance is available for osteoarthritis, juvenile idiopathic arthritis, ankylosing spondylarthritis and psoriatic arthritis in view of their different pathogeneses. The deadline for providing comments is 5 June 2012.

A revised guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/rev.4) and its appendix (EMA/CHMP/27994/2008 Rev. 1) were published on 22 December 2011. The revisions include: a more focused section on exploratory trials for cytotoxic compounds; an expanded section on conditions such as non-small cell lung cancer, prostate cancer, chronic myeloid leukaemia, myelodysplastic syndrome and haematopoietic stem cell transplantation; the role of biomarkers; and methodological issues related to the use of progression-free survival or disease-free survival endpoints. It is released for consultation until 31 May 2012.

A guideline on the evaluation of medicinal products for the treatment of bacterial infections came into effect in January 2012 (CPMP/EWP/558/95 rev 2). It details the microbiological and clinical data required to support indications, dose regimens and durations of therapy for such agents. The document is applicable to antibacterial agents which have a direct action on bacteria resulting in inhibition of growth and replication with or without a rapid bactericidal effect, and which are administered systemically. Many of the principles raised in the document might also apply to agents delivered by topical administration, inhalation or the oral route with an intended effect within the gut. The requirements do not apply to: products used for the treatment of tuberculosis; agents for systemic or inhalational use in cystic fibrosis, products that affect bacterial virulence or that indirectly inhibit the growth of some bacterial species (e.g. immunomodulators) or bacteriophages.

Non-clinical and clinical guidance continued

A draft guideline on the *'Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced-therapy medicinal products (ATMP)'* was released for consultation until June 2012 (EMA/CAT/CPWP/686637/2011). The aim of the risk-based approach in the development of ATMPs is to determine the extent of quality, non-clinical and clinical data in the marketing authorisation application generated in accordance with quality, safety and efficacy guidelines and to justify any deviation from these guidelines. The risk-based approach to development is optional. Applicants are advised to follow the methodology included in the document if such approach is applied.

A reflection paper on design modifications of gene therapy medicinal products during development was adopted on 9 February 2012 (EMA/CAT/GTWP/44236/2009). The paper intents to give some insight into the types of studies that are likely to be required in an application dossier to support the modification in the product design introduced during development.

A draft guideline on similar biological medicinal products containing interferon beta was released on 19 January 2012 (EMA/CHMP/BMWP/652000/2010). It lays down the non-clinical and clinical requirements for products claiming to be similar to another interferon beta already marketed. The deadline for providing comments to the guideline is 31 May 2012.

An ICH guideline *'S2 (R1)-Genotoxicity testing and data interpretation for pharmaceuticals intended for human use'* will come into effect in June 2012 (EMA/CHMP/ICH/126642/2008). It replaces and combines the ICH S2A and S2B guidelines. The document describes internationally agreed standards for follow-up testing and interpretation of positive results *in vitro* and *in vivo* in the standard genetic toxicology battery, including assessment of non relevant findings. It applies only to products containing new "small molecule" active substances developed as human pharmaceuticals and does not apply to biologics.

A guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products will come into effect in August 2012. (EMA/CHMP/37646/2009). It includes guidance on the studies required at different phases of drug development in genetic subpopulations that have variable systemic exposure of active substances.

The following questions and answers documents were released in March 2012:

- Q&A on the ICH guidance M3 (R2) *'Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals'* (EMA/CHMP/ICH/507008/2011). It includes clarifications on issues related to preclinical toxicity testing of fixed and non-fixed combinations.

- Q&A addressed to the Pharmacokinetics Working Party (EMA/618604/2008 Rev. 4). It includes a clarification on the requirements for demonstration of bioequivalence for generics of biphasic modified release formulations for oral use.

Pharmaceutical development guidance

A joint CHMP/CVMP draft guideline on the use of near infrared spectroscopy (NIRS) for new submissions and variations dossiers was released on 9 February 2012 (EMEA/CHMP/CVMP/QWP/17760/2009). NIRS is a technique widely used in pharmaceutical development, which includes the identification, qualification and assay of pharmaceutical starting materials, intermediates and finished products. NIRS also constitutes one of the major techniques in Process Analytical Technology (PAT) and may also be used as part of a Real Time Release Testing (RTRT) strategy. The document outlines the requirements for dossiers in which NIRS is used for qualitative and quantitative analysis or where it is used as a PAT for monitoring and controlling drug substance synthesis and finished product manufacturing processes. It is released for consultation until 31 May 2012.

Pharmaceutical development guidance continued

A revised guideline on the active substance master file (ASMF) procedure was published for consultation until 12 March 2012 (CHMP/QWP/227/02 Rev3; CVMP/134/02 Rev 3). The objective of the revisions is to have a unique version of an ASMF for one active substance valid for the whole EU, and one assessment report of the ASMF recognised by EU National Competent Authorities, the EMA and the European Directorate for the Quality of Medicines.

A draft reflection paper on the use of starting materials and intermediates collected from different sources in the manufacturing of biologics was released on 27 February 2012 (EMA/CHMP/BWP/729106/2011). It addresses the extent of the variability that may be acceptable in the early manufacturing steps of biologics which contain active substance extracted from organs, tissues or fluids from living organisms for which flexibility of sourcing in the starting materials may be needed to ensure product supply. The document also clarifies the definition of starting materials. It is released for consultation until deadline 31 August 2012.

Pharmacovigilance guidance

The first modules on good pharmacovigilance practices (GVP) were released for public consultation until 18 April 2012. GVP is a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union. They apply to marketing-authorisation holders, the EMA and regulatory authorities in EU Member States, and cover centrally authorised medicines as well as medicines authorised at national level. The modules are as follows:

- • Module I: Pharmacovigilance systems and their quality systems (EMA/541760/2011)
- • Module II: Pharmacovigilance systems master files (EMA/816573/2011)
- • Module V: Risk management systems (EMA/838713/2011)
- • Module VI: Management and reporting of adverse reactions to medicinal products (EMA/873138/2011)
- • Module VII: Periodic safety update reports (EMA/816292/2011)
- • Module VIII: Post-authorisation safety studies (EMA/813938/2011)
- • Module IX: Signal management (EMA/827661/2011)

The Agency intends to finalise these modules by July 2012, after comments from all stakeholders have been taken into account. SMEs are particularly encouraged to provide comments to the different modules.

A revised guidance on the mandatory *'Article 57(2)'* requirements for marketing authorisation holders was published on 5 March 2012. *'Article 57(2)'* of the new pharmacovigilance legislation requires that lists of all human medicines authorised in the European Union (EU) are established, based on structured data submitted by the marketing authorisation holders. These lists will assist in the coordination of pharmacovigilance activities by facilitating the identification of medicines in reports on adverse reactions. The revised documents have reduced the number of data fields required for companies to meet the legal deadline of 2 July 2012. An online data entry tool (EVWEB) to facilitate data submission by SMEs was also released. Online support, training and a dedicated helpdesk have been set up to offer assistance.

The SME office has organised a workshop on pharmacovigilance on 19 April 2012. For further information please see page 5.

Veterinary medicines guidance

A draft guideline on risk characterisation and assessment of maximum residue limits (MRLs) for biocides was issued on 20 December 2011 (EMA/CVMP/90250/2010). It presents the approach taken in the MRL evaluation of pharmacologically active substances included in biocidal products for use in animal husbandry and provides guidance on the type of data required in relation to the dietary risk assessment and MRL evaluation. The deadline for comments is 30 June 2012.

The following draft VICH guidelines were published for consultation on 20 December 2011:

- *'GL34: Biologicals: testing for the detection of mycoplasma contamination'* (EMA/CVMP/VICH/463/2002). It describes the tests to be conducted to detect the presence of Mycoplasma contamination in cell culture and in ovo origin biological products for veterinary use to ensure the absence of Mycoplasma contamination. Deadline for comments March 2012

- *'GL50: Biologicals: testing harmonisation of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use'* (EMA/CVMP/VICH/463/2002). It outlines a phased approach for the waiving of the target animal batch safety test (TABST) for inactivated vaccines with the first step to harmonize the criteria on data requirements. Deadline for comments 30 June 2012.

- *'GL51: Quality: statistical evaluation of stability data'* (EMA/CVMP/VICH/858875/2011). It provides recommendations on how to use stability data generated in accordance with the VICH guideline *'GL3(R) Stability Testing of New Veterinary Drug Substances and Medicinal Products'* to propose a retest period or shelf life in a registration dossier. Deadline for comments 30 June 2012.

A guideline on data requirements for removing the target animal batch safety test for immunological veterinary medicinal products in the European Union came into effect in January 2012 (EMA/CVMP/IWP/810769/2011). It was aligned with the revised Ph. Eur. monograph on vaccines for veterinary use which states that for an established vaccine, the routine application of the safety test may be waived by the competent authority in the interests of animal welfare when a sufficient number of consecutive batches have been produced and found to comply with the test, therefore demonstrating the consistency of the manufacturing process.

A draft guideline on the approach to establish a pharmacological acceptable daily intake (ADI) was adopted on 23 January 2012 (EMA/CVMP/SWP/355689/2006). MRLs are generally derived from ADI based on toxicological or microbiological data. However, certain substances may exert pharmacological effects in humans at exposure levels below those required to produce toxicological/microbiological effects. The guideline applies to pharmacologically active compounds and their active metabolites that may appear as residues in food producing animals when treated with a veterinary medicinal product. Setting a pharmacological ADI is not mandatory for all MRL applications and should only be considered where pharmacological effects have been identified. The deadline for comments is July 2012.

A reflection paper on risk management plans for centrally authorised veterinary medicinal products was adopted on 15 February 2012 (EMEA/CVMP/126726/2007). The provision for risk management systems is new in the field of veterinary medicines. The legal provision for risk management plans was originally developed in response to safety issues arising from the use of human medicinal products and marketing authorisation holders of products for human use are required to submit risk management plans as a routine. Following the feedback received from stakeholders it is considered appropriate to limit the scope for requiring risk management plans only to specific veterinary medicinal products. These will be products where there are identified potential or actual risks that cannot be managed or mitigated through routine pharmacovigilance or when requested by the relevant competent authority to ensure that the benefit-risk balance remains favourable.

Veterinary medicines guidance continued

Two final guidance documents will come into effect in August 2012:

- A guideline on statistical principles for clinical trials for veterinary medicinal products (EMA/CVMP/EWP/81976/2010). The guideline is similar to its counterpart in human field (CPMP/ICH/363/96) and addresses in addition specific veterinary issues.

- A reflection paper on testing strategy and risk assessment for plants (EMA/CVMP/ERA/147844/2011). The paper updates the testing strategy for plants according to the VICH guideline that enables applicants to assess the risk for plants in a 'tiered' approach while also considering the revision of the OECD 208 guideline for plant testing.

Regulatory guidance

EMA procedural advice for users of the centralised procedure for generic/hybrid applications (EMEA/CHMP/225411/2006) was updated to include information on data protection period of the reference medicinal product.

EMA pre-submission procedural advice for users of the centralised procedure (Link) was updated to include information on: evidence of proof of establishment of enterprises in the EU, pharmacovigilance system requirements, paediatric requirements, manufacture and batch release, active substance master files.

Meetings

- The next workshop for SMEs will take place on 19 April at the Agency and this year's focus will be on 'Pharmacovigilance'. Further information and registration is available under Link.

- The report and presentations of the meeting *'Ethical considerations for paediatric trials - how can ethics committees in the European Member States and the Paediatric Committee at the European Medicines Agency work together?'* held in November 2011 are now available under Link.

- The videos from the EMA/TOPRA *'Annual European Medicines Agency review of the year and outlook for 2012'* have been published (Link).

SME companies registered with the Agency

674 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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