

SME Office NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
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Pharmaceutical development guidance

Since July 2013, all active substances manufactured outside of the EU and imported into the EU should be accompanied by a written confirmation from the competent authority of the exporting country which confirms that the GMP standards and control of the manufacturing site are equivalent to those in the EU. Companies should make sure that the active substance manufacturers they are working with are registered with their local authorities. Exporting countries with a regulatory framework equivalent to that of the EU will not need to issue written confirmations: Australia, Japan, Switzerland and the United States are currently meeting these criteria.

A guideline on starting materials and intermediates collected from different sources, which are used in the manufacturing of non-recombinant biological medicinal products will come into effect on 1 December 2013 ([EMA/CHMP/BWP/429241/2013](#)). It discusses to what extent variability in early manufacturing is acceptable for non-recombinant biologics containing active substances extracted from organs, tissues or fluids from living organisms, either of animal or plant origin, and for which flexibility in the sourcing in the starting materials may be needed to ensure product supply.



A guideline on pharmaceutical development of medicines for paediatric use will come into effect on 15 February 2014 ([EMA/CHMP/QWP/805880/2012 Rev. 2](#)). It sets out the principles to be considered during the pharmaceutical development of all paediatric medicines (generic, innovative; existing or new) in marketing-authorisation applications or variations/extensions thereof. The principles also apply to paediatric investigation plan (PIP) applications depending on the phase of the development of the product.

Clinical development guidance

A revised guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence will come into effect on 1 January 2014 ([CPMP/EWP/18/01/Rev. 1](#)). It has been revised with respect to registration requirements for overactive bladder syndrome and stress incontinence. Specific guidance on paediatric requirements, male incontinence and tissue engineered products are also included.

A draft guideline on the adjustment for baseline covariates was released for consultation until 31 December 2013 ([EMA/295050/2013](#)). It provides advice on how to address baseline covariates in designing, analysing and reporting confirmatory randomised trials.

A revised guidance on the clinical investigation of products for the treatment of asthma was released for consultation until 31 December 2013 ([CHMP/EWP/2922/01 Rev.1](#)). It was updated to take into account updated international clinical recommendations, now focussing on a control-based management, and to include a section on paediatrics.

A revised guidance on the evaluation of agents for irritable bowel syndrome has been released for consultation with a deadline for comments of 15 January 2014 ([CPMP/EWP/785/97 Rev. 1](#)).

It will replace the existing points to consider document on the topic. It was updated in relation to the selection of patient population and the primary endpoints in confirmatory trials, with dedicated sections added on special patient groups (gender based, children and elderly) and geographic regions.

A draft guideline on the clinical investigation of products for the treatment of amyotrophic lateral sclerosis was released for consultation until 31 January 2014 ([EMA/CHMP/40105/2013](#)). It replaces and updates the previous points to consider document on the topic, in relation to the design of studies, the choice of outcome parameters and the clinical relevance of functional tests of disability and their relationship to survival.

A draft guideline on medicinal products developed in the treatment of hypertension was released for consultation until 31 January 2014 ([EMA/CHMP/29947/2013/Rev. 4](#)). The document was revised to include more guidance on the collection of long-term safety data and to clarify the situations in which outcome studies might be required to detect potential long-term effects on mortality and morbidity.

Multidisciplinary guidance

A reflection paper on the management of clinical risks deriving from insertional mutagenesis, was published on 1 August 2013 ([EMA/CAT/190186/2012](#)). It discusses the factors contributing to the genotoxicity of vector integration, the strategies to reduce the risk and the assays to evaluate vector oncogenesis at the pre-clinical and clinical level.

A draft ICH guideline Q3D on elemental impurities was released for consultation until 31 December 2013 ([Link](#)). Elemental impurities may be added intentionally during synthesis or present as contaminants (e.g. through interactions with processing equipment). The document elaborates on the evaluation of the toxicity data, the establishment of a Permitted Daily Exposure (PDE), and the development of controls to levels at or below the PDE.

A reflection paper on nanomedicines was adopted on 15 August 2013. It elaborates on development issues related to the effect of nano-coating on the stability, pharmacokinetics and biodistribution of the medicine and the potential interaction of the coating with other molecules ([EMA/325027/2013](#)).

A draft reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product, was released for consultation until 28 February 2014 ([EMA/CHMP/SWP/620008/2012](#)). This document sets out quality, non-clinical and PK clinical comparative data needed to support a marketing authorisation for such products.

Pharmacovigilance

Update guidance was released on:

- Post Authorisation Safety Study (PASS): guidance on the format and content of the final study report ([EMA/48663/2013](#)); questions and answers ([Link](#))
- Risk-management plans (RMPs): changes applying as of 1 August 2013 on RMPs update requirements (move from an automatic fixed-time basis to lighter risk-based approach) and clarifications on what should be included under the section on 'Safety concerns' ([Link](#)). All the related guidance documents on the format of RMPs have been updated to reflect this change. Updates to GVP module V and annex 1 are scheduled for update later in 2013.



A technical guide for implementing the standard adopted by ICH for the electronic transmission of Individual Case Safety Reports (ICSRs) according to the ICH E2B(R3) message standard was released in July 2013. It is intended for use by system developers, IT professionals, system implementers and system users who need to understand the technical requirements for constructing and using valid electronic messages to transmit ICSRs ([Link](#)).

Guidance for veterinary medicines



A revised policy for classification and incentives for veterinary medicinal products indicated for minor use minor species/ limited markets is applicable as of 1 September 2013 ([EMA/429080/2009 - Rev.1](#)). The policy has been revised to direct incentives to those products that have the potential to be of most benefit to animal health.

A guideline setting out the data requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) will come into effect on 1 February 2014 ([EMA/CVMP/IWP/594618/2010](#)). It compiles into a single document the existing guidelines:

- Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010 3/12).
- Guideline on requirements for concurrent administration of immunological veterinary medicinal products (EMA/CVMP/550/02).
- Note for guidance: Requirements for combined veterinary vaccines (CVMP/IWP/52/97).

Regulatory and procedural guidance

Updated guidance for centralised dossiers was published on:

- Pre-authorisation guidance on topics related to the active substance master files, and MA dossier validation ([Link](#))
- Use of digital signatures in documents related to scientific advice for human medicines, orphan medicines and paediatric-medicine procedures ([Link](#)).
- Questions and answers on eCTD ICH guideline M8 ([Link](#)).
- Post-authorisation guidance on topics related to post-authorisation measures, transfer of MA dossier, periodic safety update reports, transparency, risk-management plan ([Link](#)).

Updated information on fees were released relating to protocol assistance, orphan advanced-therapy medicinal products from applicants other than micro, small and medium sized enterprises, and fee incentives for pharmacovigilance-related variations for products for human use ([Link](#)).

New variations guidelines have been introduced and apply for human and veterinary medicines as of 4 August 2013. Detailed information can be found in:

- Questions and answers on the implementation ([Link](#)).
- Updated post-authorisation guidance ([Link](#)).
- Updated variations application form ([Link](#)).

An overview of the guidelines which include information on SmPC recommendations for quality, non-clinical and clinical sections was published ([EMA/813125/2012 rev. 2](#)).

Meetings

The report of the following meeting has been released:

- Workshop on development of new antibacterial medicines held in October 2012 ([Link](#)).

The following workshops have been announced:

- Joint EMA/EDQM workshop on characterisation of new clotting-factor concentrates (factor VIII and factor IX), EMA, London, UK, 28-29 Nov-2013 ([Link](#)).
- Workshop on biosimilars organised as part of the public consultation exercise on a series of recently issued guidelines on biosimilars, EMA, London, UK, 31 October 2013 ([Link](#)).

Registered SMEs

Currently, 1,202 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.

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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