



SME Office

NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
Published four times a year by the European Medicines Agency.

An agency of the European Union



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Pharmaceutical development guidance

A revised guideline on the use of bovine serum in the manufacture of human biological medicinal products will come into effect on 1 December 2013 ([EMA/CHMP/BWP/457920/2012 rev 1](#)). The sections on the testing requirements for BVDV bovine viral diarrhoea virus (BVDV) and anti-BVDV antibodies have been revised to align them with the requirements applied for immunological veterinary products.



A guideline on the quality of biological active substances produced by transgene expression in animals will come into effect on 1 December 2013 ([EMA/CHMP/BWP/151897/2013](#)). It focuses on the quality aspects of active substances produced by the expression of one or more transgenes located in the nuclear genomes of animals, the selection, generation and control of the production animals and evaluation of freedom from adventitious agents.

An amended guideline on the active substance master file procedure for human and veterinary products was published on 10 June 2013. The document was updated to provide clarifications on manufacturing sites and details on the salt form, water content and grade of the active substance ([EMA/CVMP/134/02 Rev 02](#)).

A draft guideline on the quantitative composition and labelling of biologics containing modified proteins as active substance was released for consultation until 1 October 2013 ([EMA/CHMP/BWP/85290/2012](#)). Modified proteins refer to proteins intentionally modified (e.g. conjugated, pegylated or amino acid modifications) vs. the parent non-modified proteins. The document discusses the approach taking into account the product class, the clinically established declared value (e.g. international unit, mass unit) for the non-modified product, the method of assay and the relevance of the potency assay.

The following questions and answers were updated:

- Quality of medicines which now includes a new section on quality by design and application of real-time release testing ([Link](#)).
- Good manufacturing practice which includes information on audit of active substance manufacturers ([Link](#)).
- Quality of herbal products ([EMA/HMPC/41500/2010 Rev.2](#)).

Non-clinical development guidance

A draft 'ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk' was released for consultation until 20 June 2013 ([EMA/CHMP/ICH/83812/2013](#)). It provides a practical framework for the identification, categorisation, qualification and control of mutagenic impurities.

A draft reflection paper on the use of methyl- and propylparaben as excipients in human medicines for oral use was released for comments until 31 October 2013 ([EMA/CHMP/SWP/272921/2012](#)). Parabens are currently listed for their allergic potential in the guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev.1). Possible endocrine-disrupting effects are discussed. The paper may trigger further revision of the guideline on excipients in relation to these parabens.

A draft guideline on the use of phthalates as excipients in human medicinal products was published for consultation until 31 October 2013 ([EMA/CHMP/SWP/362974/2012](#)). Literature data in animals show that certain phthalates are associated with effects on reproduction and development, related to their hormonal properties. Available human data on the impact of phthalate exposure are limited. The document provides recommendations for daily exposure in light of preclinical evidence aiming at reducing the content of some phthalates in medicines.

Clinical development guidance

A guideline on the investigation of medicinal products for the prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery will come into effect on 30 November 2013 ([EMA/CHMP/325170/2012](#); former CPMP/EWP/707/98 Rev. 1 corr). The document was revised to include updated definitions of major and minor bleeding and secondary endpoints related to the reporting of surgical blood loss.



A guideline on products developed for the treatment of depression will come into effect on 1 December 2013 ([EMA/CHMP/185423/2010 Rev. 2](#); previously CPMP/EWP/518/97, Rev. 1). The revisions clarify the requirements for long-term efficacy data and specify the data requirements in children, adolescents and the elderly.

A draft guideline on medicinal products developed for chronic primary immune thrombocytopenia was released for consultation until 31 August 2013 ([EMA/CHMP/153191/2013](#)). The document sets out the clinical requirements for demonstrating efficacy and safety in adults and paediatric patients.

A draft guideline on similar biological medicinal products was posted for consultation until 31 October 2013 ([CHMP/437/04 Rev. 1](#)). The document addresses the concepts for the application of the biosimilar approach, the choice of the reference product and the general principles of establishing biosimilarity.

A draft guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance was released for consultation until 30 November 2013 ([EMA/CHMP/BMWP/42832/2005 Rev. 1](#)). The document was revised to include specific guidance on e.g. the risk-based approach for the non-clinical program, the pharmacodynamic markers for clinical comparability, study design, surrogate endpoints, immunogenicity, data bridging and extrapolation of indications.

A guideline on the development of products for the treatment of pain was published for consultation until 30 November 2013 ([EMA/CHMP/970057/2011](#)). It replaces and updates the two separate guidelines on neuropathic and nociceptive pain. Guidance is provided on study design, efficacy and safety endpoints and target populations, including children and the elderly. As many aspects are now considered common in both types of pain, the two original guidelines have been combined.

Guidance on Pharmacovigilance

For ease of access and navigation, GVP modules are now grouped on a dedicated webpage ([Link](#)). Definitions are included under annex I, templates referenced in annex II, other applicable pharmacovigilance guidance under Annex III, relevant ICH guidance in Annex IV and abbreviations in annex V. Information and templates relating to risk management plans are also available online [Link](#).

The following good pharmacovigilance practices (GVP) modules have recently been released:

- Final module X on additional monitoring ([EMA/169546/2012](#)). The concept of additional monitoring originates from the need to enhance adverse drug reaction reporting for newly authorised products. These products will be identifiable by an inverted equilateral black triangle and included in a public list maintained by the EMA. Module X includes general principles for assigning the additional monitoring status and communication related aspects.
- Revised module II on the pharmacovigilance system master file. It contains changes relating to the requirements for herbal and homeopathic medicinal products and updated legal references ([EMA/816573/2011 Rev 1*](#)).
- Revised module VIII on post-authorisation safety studies (PASS) ([EMA/813938/2011 Rev 1](#)) and addendum on Member States requirements for PASS ([EMA/395730/2012 Rev 1](#)). It includes clarifications on the scope of the guidance for EU and non-EU studies, the classification of a study as a PASS and information on study registration.
- Draft module XVI on risk-minimisation measures and selection of tools and effectiveness indicators ([EMA/204715/2012](#)) for consultation until 5 August 2013. Most safety concerns are addressed by routine risk minimisation measures (see module V). For some risks, however, additional risk minimization measures will be necessary and module XVI provides further information. Further guidance is also available in a position paper on potential medication errors in the context of benefit-risk balance and risk-minimisation measures ([EMA/CHMP/277591/2013](#)).
- Draft module VI on the management and reporting of adverse reactions ([EMA/873138/2011 Rev 1](#)) for consultation until 5 August 2013. Following an initial public consultation the document was revised to clarify the reporting requirements for marketing authorisation holders (MAHs) or academic sponsors on behalf of MAHs, of suspected adverse reactions occurring in non-interventional studies. It also provides more guidance on timelines for the reporting of valid case reports, the reporting from PASS as well as how to handle different languages.
- Draft module on vaccines ([EMA/488220/2012](#); [Annex](#)). This product-specific module applies to vaccines used for pre- and post-exposure prophylaxis of infectious diseases and does not cover 'therapeutic' vaccines (e.g. viral-vector based gene therapy, tumour vaccines). Once the GVP module is finalized, the CHMP pharmacovigilance guideline for vaccines ([EMA/CHMP/PhVWP/503449/2007](#); [Link](#)) will no longer be applicable.
- Draft module VII on periodic safety update reports [PSUR] ([EMA/816292/2011 Rev. 1](#)). The module was updated following the finalisation of the ICH-E2C(R2) guideline on 'Periodic Benefit-Risk Evaluation Report (PBRER)'. Updated information on NCA/EMA requirements for the submission of PSUR during the transitional period is included in [EMA/413951/2012-Rev.4](#) and information on EU reference dates and frequency of submission of PSURs is provided in an explanatory note ([Link](#)). Information on how to submit PSURs for an EU single assessment of substances contained in both centrally and nationally authorised products has been published ([Link](#)).



Marketing authorisation holders of centrally and nationally authorised human medicines will have the obligation to notify the EMA and/or Member States the reasons for the cessation, suspension, withdrawal or non-renewal of marketing authorisations. The notification requirements apply from 5 June 2013 for centrally authorised medicines and from 28 October 2013 for nationally authorised medicines. More information is available on the EMA website ([Link](#)).

Guidance for veterinary medicines



A guideline on the development of veterinary medicinal products containing antimicrobials was released for consultation until 30 November 2013 ([EMA/CVMP/261180/2012](#)). The document was revised to provide recommendations on the design and conduct of pre-clinical and clinical studies (e.g. data to support a metaphylaxis claim, comparators and endpoints).

A recommendation to marketing authorisation holders of veterinary vaccines to update the authorisations to remove the target animal batch safety test (TABST) following removal of the requirement from the European Pharmacopoeia monographs was published on 15 May 2013 ([Link](#)).

A revised policy on minor-use-minor-species/limited-market was adopted on 13 June 2013. The policy has been revised to target the related fee incentives to products indicated for food producing species only ([Link](#)).

The following pharmacovigilance questions and answers were released on 19 April 2013:

- Management and assessment of periodic safety update reports (PSURs) ([EMA/CVMP/PhVWP/12661/2009-Rev.3](#)).
- Serious non-fatal adverse events and reporting rules ([EMA/CVMP/PhVWP/303762/2012](#)).
- Adverse event reporting ([EMA/CVMP/PhVWP/145186/2013](#)).

Regulatory and procedural guidance

From 1 March 2014, the use of the *eSubmission Gateway* or *web client* will become mandatory for all electronic Common Technical Document (eCTD) submissions through the centralised procedure. After this date, the EMA will no longer accept these submissions on CD or DVD. This applies to all marketing-authorisation and variation applications for human medicines. The *eSubmission Gateway* is an electronic submission channel launched in 2012 to allow secure web submission of all types of eCTD applications for human medicines. The *eSubmission web client* was launched in 2013 to complement the Gateway and is aimed at applicants with lower transmission volumes such as SME companies. Applicants are invited to register to use the *eSubmission Gateway* or the free web-client solution as soon as possible. Further information is available under [Link](#) and [eSubmission Gateway or web client](#).

The following updated regulatory guidance for centralised dossiers has been published:

- Paediatric investigation plan: notification of discontinued paediatric developments within a paediatric investigation plan ([Link](#)).
- Pre-authorisation: rapporteurship, GMP/GCP fees, EU risk management plan, pharmacovigilance system, dossier requirements ([EMA/339324/2007](#))
- Post-authorisation: type IB fees, rapporteurship for type II/extensions dossiers, rapporteurship and dossier requirements for type II/worksharing, invented names, transfer of MA dossier, annual reassessment, renewals, annual review of conditional marketing authorisations, PASS, PSUR, transparency, pharmacovigilance system, post-authorisation measures (PAMs) ([EMA-H-19984/03 Rev 28](#))
- Generic/hybrid applications: rapporteurship, dossier requirements, evaluation, EU risk management plan, pharmacovigilance system ([EMA/CHMP/225411/2006](#)).
- Biosimilars: rapporteurship, dossier requirements, evaluation, EU risk management plan, pharmacovigilance system ([EMA/940451/2011](#)).
- MA transfers: name change, qualified person, fees, electronic submissions ([Link](#)).
- Requirements for the submission of product-information in Croatian for initial marketing authorisations and extensions (human and veterinary products) ([Link](#)).

A guideline on the acceptability of names for human medicines processed through the centralised procedure was released for consultation until 30 August 2013 ([CPMP/328/98, Revision 6](#)). The document was revised to clarify the review criteria applied and international

non-proprietary name issues.

A major update of the application form for marketing authorisations applications (centrally and nationally authorised) was released in May 2013 by the EC ([Link](#); [Notice to applicants](#)). The amendments relate to section 1 (scope, ATMP rapporteurship, orphan market exclusivity, paediatric requirements), section 2 (information on containers, devices; proof of payment/billing address—for NCAs only; qualified person for pharmacovigilance; D.U.N.S. credit number), section 4 (information on MA refusals) and annexes (justification to support 'new active substance' claim for applications submitted under Art. 8(3) of Directive 2001/83/EEC; deletion of CV of qualified Person for PhV).

An EC Guidance on variations for human and veterinary use products for centrally and nationally authorised products will apply as of 4 August 2013 ([Link](#)). It was updated to include the new categories of variations and procedural aspects. It replaces the procedural guideline from chapter 5 of Volume 2A of the Notice to Applicants and the classification Guideline from volume 2C of the Notice to Applicants.

A guideline on dossier requirements for herbal medicinal products in line with the Common Technical Document (CTD) format was adopted on 13 May 2013 ([EMA/HMPC/71049/2007 Rev. 1](#)). It was revised to include information on the content of Module 3 and clarifications on the location of relevant parts of the documentation. Updated regulatory questions and answers on herbals have also been released recently ([EMA/HMPC/345132/2010 Rev.2](#)).

Meetings and reports

The reports and video content of the following meetings have been released:

- SME Workshop ([Link](#))
- Workshop on paediatric investigation plans in type-2 diabetes mellitus ([Link](#))
- Workshop on process validation for the manufacture of biotechnology-derived active substances ([Link](#))
- Workshop on correlates for the protection and serological assays for influenza vaccines ([Link](#)).
- Training session on the new pharmaceutical legislation ([Link](#))
- Workshop on medication errors ([Link](#))
- Workshop on patient-support programmes and market-research programmes ([Link](#))

The following workshops have been announced:

- Workshop on the clinical investigation of new medicines for the treatment of multiple sclerosis, EMA, London, 17 October 2013 ([Link](#))
- Workshop on EMA-HTA parallel scientific advice in drug development, EMA, London, 26 November 2013 ([Link](#))

An SME workshop for veterinary medicines will take place on Thursday 07 November 2013 at the European Medicines Agency (EMA) in London. Registration and further information will be announced in September 2013.

The EC has recently released a report on the experience acquired as a result of the application of the paediatric regulation. The report titled 'Better medicines for children – from concept to reality' analyses the successes and suggests improvements to the implementation of the regulation ([Link](#)).

Publication and access to clinical-trial data

A draft EMA policy on publication and access to clinical-trial data has been released for consultation until 30 September 2013 ([Link](#)). It provides details on how the EMA proposes to move towards proactive publication of clinical-trial data for the medicines it has assessed. The document was drafted following consultation with external stakeholders and European bodies and complements the existing policy on access to documents. Further information is available under [Link](#).

Registered SMEs

Currently, 1,156 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 \(veterinary medicines\)](#)

Contact the SME Office

E-mail: smeoffice@ema.europa.eu

Tel: +44 (0)20 7418 8575/8463

Fax: +44 (0)20 7523 7040

European Medicines Agency

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom

Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416

E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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