



SME Office NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
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IN THIS ISSUE

Non-clinical and clinical development guidance	1
Guidance on pharmacovigilance (Human medicines)	2
Regulatory and procedural guidance	
Quality guidance	3
Guidance for veterinary medicines	4
Meetings & reports	5
Registered SMEs	5
Contact details	6

Non-clinical and clinical development guidance

A revised guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance will come into effect on 1 July 2015 ([EMA/CHMP/BMWP/42832/2005 Rev1](#)).

The current revision covers a stepwise conduct of non-clinical and clinical studies and discusses a number of topics such as the use of pharmacodynamic markers, study design, patient population, choice of surrogate and clinical endpoints, clinical safety, risk management plan, pharmacovigilance and extrapolation of safety and efficacy.

A revised guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues will come into effect on 1 September 2015 ([EMA/CHMP/BMWP/32775/2005 Rev. 1](#)).

Compared to the previous version, intermediate-, long-acting insulin preparations and insulin analogues have been included in its scope, a risk-based approach for non-clinical in vivo studies has been introduced and more detailed guidance on the design, study population, insulin doses and endpoints of the insulin clamp study is given.

An addendum to the guideline on clinical investigation of medicinal products in the treatment of hypertension ([EMA/238/1995/Rev. 3](#)) will come into effect on 1 September 2015 ([EMA/CHMP/206815/2013](#)).

The document highlights paediatric specific aspects of development and design of clinical studies, in particular in secondary forms of hypertension, methods to establish dosing recommendations and paediatric safety.

A guideline on the clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis will come into effect on 1 September 2015 ([EMA/CHMP/51230/2013](#)).

It provides guidance on inclusion and exclusion criteria, concomitant use of other medicines, clinical efficacy and safety endpoints.

A guideline on adjustment for baseline covariates in clinical trials will come into effect on 1 October 2015 ([EMA/CHMP/295050/2013](#)). It provides advice on how to address important baseline covariates in designing, analysing and reporting confirmatory randomised trials.

A guideline on the clinical investigation of medicinal products for the treatment of multiple sclerosis will come into effect on 1 October 2015 ([EMA/CHMP/771815/2011, Rev. 2](#)). It focuses on treatments aimed to modify disease progression and discusses study design, endpoints and trials duration.

A final reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product was adopted by the CHMP on 26 March 2015 ([EMA/CHMP/SWP/620008/2012](#)). It discusses the data requirements for nano-sized colloidal intravenous iron-based preparations developed as a treatment for iron deficiency with reference to an innovator product.

A Questions & Answers document on the '*Guideline on the environmental risk assessment of medicinal products for human use*' has been released for public consultation until 30 June 2015 ([EMA/CHMP/SWP/44609/2010 Rev. 1](#)). It provides clarifications on the implementation of the environmental risk assessment guideline ([EMA/CHMP/SWP/4447/00](#)).

A draft guideline on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease has been released for consultation until 30 September 2015 ([EMA/CHMP/41230/2015](#)). The update includes considerations on initial and extended treatment of venous thromboembolism, treatment of deep and superficial vein thrombosis, imaging techniques, controls, definition of bleeding events and description of methods for measuring blood loss and timing for collection of data.

The Agency has published on 7 February 2015 a qualification opinion on the in-vitro hollow fiber system model of tuberculosis (TB) ([EMA/CHMP/SAWP/47290/2015 Corr.](#)). It is qualified to be used in anti-TB drug development programs as an additional and complementary tool to existing methodology to inform dose selection and treatment regimen, including combinations of 2 or more TB drugs. The model can be used in regulatory submissions throughout the drug development process for a product, especially for more informed design and interpretation of phase I, II and III clinical studies.

On 22 January 2015, the Agency's Pharmacokinetics Working Party published a revised Questions & Answers document ([EMA/618604/2008 Rev. 11](#)); covered topics include orally inhaled medicinal products and on the pharmacokinetics of medicinal products in patients with impaired hepatic function guideline.

The Agency has updated a Questions & Answers document on the withdrawal of the '*Guideline on pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A)*' ([EMA/CHMP/SWP/1991104/2014 corr 1](#)). Its aim is to provide clarifications on how to obtain information on pharmacokinetics from other sources such as regulatory ICH guidelines.

Pharmacovigilance fees

On 10 March 2015, the Agency has published an explanatory note on the fees payable to the Agency for its monitoring of the safety of medicines authorised in the European Union.

Pharmacovigilance Fee	Micro enterprises	Small and medium-sized enterprises
Periodic Safety Update Report	Exempt	60% of the applicable fee or share of fee
Post-authorisation Safety Study	Exempt	60% of the applicable fee or share of fee
Pharmacovigilance-related Referral	Exempt	60% of the applicable fee or share of fee
Annual fee for IT systems and literature monitoring	Exempt	60% of the applicable fee

The document describes types of fees and fee exemptions and explains how the Agency charges and collects fees from marketing-authorisation holders of medicinal products for human use. Fee reductions and exemptions are in place for SMEs (see picture above).

[Information on pharmacovigilance fees;](#)
[Link to explanatory note on pharmacovigilance fees](#)

Guidance on pharmacovigilance for human medicines

A technical implementation guide ([EMA/51938/2013; Q&A document](#)) relating to ICH guideline E2B (R3) was released for information by the EU Regulatory Network in January 2015. This guide is based on the ICH E2B (R3) guideline and the corresponding ISO ICSR standard as referred to in Commission Implementing Regulation (EU) No. 520/2012. It describes the additional EU specific requirements to generate a valid ICSR (also referred to as Safety Message) and Message Acknowledgment to implement EN ISO ICSR 27953-2:2011 in accordance with ICH E2B(R3). It will apply with the use of the ISO ICSR standard as of 1 July 2016.

On 23 February 2015, the Agency has published a document 'Data submission of authorised medicines in the European Union - Outlines on Article 57(2) of Regulation (EC) No 726/2004' ([EMA/471367/2014, Rev. 11](#)). It provides an overview on the Article 57 data work-flow, data management, governance aspects, future use and evolution of the data and addresses clarifications requested by the EU Regulatory Network and Agency's stakeholders.

Regulatory and procedural guidance

The EU Regulatory Network has published guidance on the application form for type I variations ([EMA/233564/2014](#); [CMDh/EMA/133/2010](#)). It will help applicants preparing variation applications to be submitted to regulatory authorities.

Pre-authorisation ([EMA/339324/2007](#)) and post-authorisation ([EMEA-H-19984/03 Rev. 47](#)) procedural advice for users of the centralised procedure were updated in relation to:

- Orphan drugs
- Mock-ups and specimens
- Good clinical practice (GCP) inspections
- Good laboratory practice (GLP) compliance
- The pharmacovigilance system
- Qualified Person for Pharmacovigilance (QPPV)
- Periodic safety update reports (PSURs)
- Invented name
- Variations (worksharing, type II variations, group-
ing).

Guidance for generic/hybrid applications and biosimilar applications were revised on GCP inspections, GLP compliance and update of product information after PSUR ([EMEA/CHMP/225411/2006](#), [EMA/940451/2011](#)).

Questions and Answers webpages relating to Good manufacturing practice ([Link](#)) and Quality of medicines ([Part 1](#), [Part 2](#)) were also updated in relation to the use of metal detectors in manufacturing processes, inspections of active substance manufacturers, impurities in active substances and finished products.

The EU Regulatory Network has published a revised reference document 'Packaging 'blue-box' requirements and additional information on labelling/package leaflet for products authorised via national, mutual recognition, decentralised or

centralised procedures' ([EMA/CMDv/391895/2012](#)). The blue-box is a colour-coded label element on the retail packaging of pharmaceutical products wherein country-specific regulatory data must be printed.

The Agency has published revised guidance related to paediatric investigation plans (PIPs) to reflect recent changes to the European Commission's guideline on PIPs ([Link](#)). The guidance documents relate to:

- The procedures for submission of PIP/waiver applications ([Link](#))
- Re-examination ([EMA/23604/2008 Rev.1](#))
- Compliance check ([EMA/PDCO/179892/2011 Rev. 2](#)).

Quality Guidance

An ICH Q3D Guideline on Elemental Impurities ([EMA/CHMP/ICH/353369/2013](#)) will come into effect in June 2016

(for new marketing authorisation applications) and December 2017

(for authorised medicinal products). ICH Q3D aims at establishing standards for limiting these elemental impurities through the application of a risk-based approach to control elemental impurities in drug products. The EMA has also released recommendations for implementing this newly adopted international standard ([EMA/CHMP/QWP/109127/2015](#)).



The Agency has released a concept paper on the need to revise the 'Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials' (Concept paper [EMA/CHMP/QWP/126334/2015](#); guideline [CHMP/QWP/185401/2004](#)) for consultation until 30 June 2015. It addresses the need to update the guideline in line with the new Regulation (EU) No. 536/2014 on clinical trials.

Guidance for veterinary medicines

A draft scientific guideline VICH GL54 'Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish an acute reference dose' was released for consultation until 15 August 2015 ([EMA/VICH/699251/2010](#)). It addresses the nature and type of data and studies to determining an acute reference dose for residues of veterinary drugs.

A guideline on risk characterisation and assessment of maximum residue limits (MRL) for biocides will come into effect on 1 August 2015 ([EMA/CVMP/SWP/90250/2010](#)). Its purpose is to present the approach taken in the MRL evaluation of pharmacologically active substances included in biocidal products for use in animal husbandry and to provide guidance on the type of data required in relation to the dietary risk assessment and MRL evaluation.

Two scientific guidelines related to studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals will come into effect in January 2016.

- VICH GL48, which focuses on marker residue depletion studies to establish product withdrawal periods and aims to provide study design recommendations to facilitate the acceptance of the generated residue depletion data ([EMA/CVMP/VICH/463199/2009](#))
- VICH GL49, which addresses the validation of analytical methods used in residue depletion studies, provides a description of the criteria suitable for the validation of analytical methods used in veterinary drug residue depletion studies ([EMA/CVMP/VICH/463202/2009](#)).

A guideline on the procedure to be followed when a batch of a vaccine finished product is suspected to be contaminated with bovine viral diarrhoea virus (BVDV) has been released for public consultation until 30 April 2015 ([EMA/CVMP/IWP/205351/2006-Rev.1](#)). It outlines the procedure to be followed by the Competent Authorities when a batch of a vaccine is suspected to be contaminated with BVDV.

On 15 January, the Agency adopted a 'Reflection paper on the risk of antimicrobial resistance transfer from companion animals' ([EMA/CVMP/AWP/401740/2013](#)). Public health risks associated with the transfer of antimicrobial resistance from companion animals are reviewed in this document, which also discusses the need for data in applications relating to new

compounds, new species or indications for existing compounds.

A draft document titled 'Principles on assignment of defined daily dose for animals and defined course dose for animals' ([EMA/710019/2014](#)) was released for public consultation until 13 May 2015. It describes the approach suggested for the assignment of defined daily dose for animals (DDDA) and defined course dose for animals (DCDA) for antimicrobial veterinary medicinal products (VMP).



The Agency has released for public consultation two guidelines related to the assessment of antimicrobials for use in veterinary medicines:

- The first guideline focuses on the assessment of the risk to public health resulting from the use of antimicrobial substances in food-producing animals ([EMA/CVMP/261180/2012](#)); deadline for comments by 31 May 2015.
- The second guideline is a revised CVMP guideline for the demonstration of efficacy for veterinary medicines containing antimicrobial substances ([EMA/CVMP/AWP/706442/2013](#)); deadline for comments by 31 August 2015. It aims to provide guidance on the development of new veterinary antimicrobials while taking into account the risk of development of antimicrobial resistance and the need to promote the responsible use of these substances.

A guideline on the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats has been released for public consultation until 30 September 2015 ([EMA/CVMP/EWP/005/2000 - Rev.3](#)). It includes information on the testing of veterinary antiparasitic products containing substances with insect growth regulating properties.

A draft reflection paper on poorly extractable and or non-radiolabelled substances has been released for public consultation until 31 August 2015 ([EMA/CVMP/ERA/349254/2014](#)). It aims to identify the issues which can arise when performing an 'OECD 307' study (aerobic and anaerobic transformation in soil) with poorly extractable and/or non-radiolabelled substances.

A scientific guideline VICH GL53 '*Electronic exchange of documents: electronic file format*' will come into effect in February 2016 ([EMA/CVMP/VICH/758781/2013](#)). It is intended to provide recommendations on electronic file format specifications for individual and collections of multiple related documents that need no subsequent editing and are used for electronic exchange between industry and regulators in the context of regulatory approval of veterinary medicinal products.

Meetings and reports

The reports and / or videos of the following meetings have been published:

- **7 November:** European Medicines Agency workshop on the investigation of subgroups in confirmatory clinical trials; ([Link](#))
- **15 December:** Workshop on development pathways for advanced-therapy medicinal products. ([Link](#))
- Annual SME Report 2014 ([Link](#)).

Registered SMEs

Currently, 1181 companies have SME status assigned by the Agency. The names and profiles of these companies 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.

Early dialogue with the EMA is key to success

To support SMEs in the development of their medicines and increase their chance of success at the marketing-authorisation stage, various support tools are provided by the EMA. These tools promote interaction and dialogue with the Agency from the very early stages of medicine development and throughout the medicine's lifecycle.

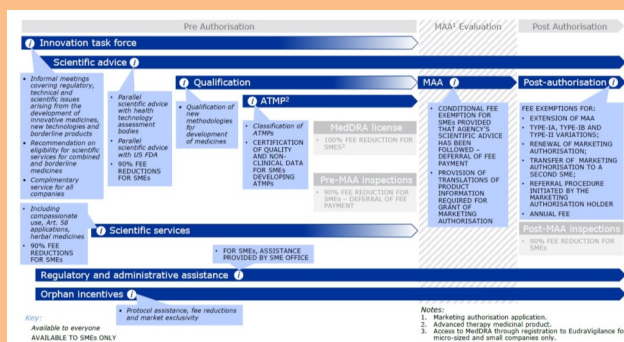


Image: Overview of support provided to medicines developers by the EMA (click on image for more information)

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;
- setting up briefing meetings to discuss regulatory strategy;
- 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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