



SME Office NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
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Guidance on pharmacovigilance for human medicines

PSUR Repository

The central repository for safety reports is a new tool introduced by the EU pharmacovigilance legislation that is intended to facilitate the exchange of information on the safety of centrally and nationally authorised medicines between regulatory authorities and pharmaceutical companies. It will become mandatory on 13 June 2016. Further details on the repository including, submission and format requirements, and implementation aspects requirements are available under [PSUR, eSubmission Gateway/ Web Client website, CMDh webpage](#).

Medical Literature Monitoring

The Medical Literature Monitoring service became fully operational on 1 September 2015. The EU pharmacovigilance legislation gave EMA responsibility for the monitoring of selected medical literature for a defined list of active substances used in medicines and for entering identified reports of suspected adverse reactions in EudraVigilance. The service aims at reducing duplication of reporting from pharmaceutical companies, and improving the safety monitoring of medicines by enhancing the quality and

consistency of data reported in EudraVigilance. Further information on the substance groups, journals covered by the monitoring, including a guide and a training video material are available under the [monitoring of medical literature](#).

Scientific advice on post-authorisation safety studies (PASS)

A 12-month pilot program to encourage scientific advice for post-authorisation safety studies (PASS) was launched in July 2015. This optional procedure aims at improving the design of studies intended to collect further information on the safety of a marketed medicine. This pilot program focuses on non-imposed PASS, i.e. studies which are not a condition to the marketing authorisation ([Link](#)). Further details are available in the [Questions & Answers](#).



The following guidance documents were updated:

- Good Pharmacovigilance Practices (GVP) - Module IV, on pharmacovigilance audits (clarification on the audit definition) ([EMA/228028/2012 Rev 1](#)).
- Questions & Answers documents on electronic submission of Article 57(2) data ([EMA/159776/2013](#)).
- EXTENDED EudraVigilance Medicinal Product Dictionary (XEVMPD) Data-Entry Tool (EVWEB) user manual ([Link](#)).

Clinical Trials Regulation, GCP, GMP

The European Commission has released for consultation until 24 November 2015 the following documents relating to the implementation of the new Clinical Trials Regulation (No 536/2014):

- Good clinical practice (GCP) inspection procedures and inspector qualifications and training requirements ([Link](#))
- Principles and guidelines of good manufacturing practice (GMP) for investigational medicinal products (IMP) ([Link](#))
- Good manufacturing practice for investigational medicinal products for human use ([Link](#)).

The Good Clinical Practice guideline (ICH E6) addendum has been released for public consultation until 3 February 2016 ([EMA/CHMP/ICH/135/1995](#)). It has been amended to encourage more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity.

The European Commission has released for consultation a document on good manufacturing practice (GMP) requirements for advanced therapy medicinal products (ATMPs) intended to be used in clinical trials or for commercial distribution in accordance with the terms of a marketing authorisation ([Link](#)). The deadline for comments is 12 November 2015.

A Questions & Answers document on ICH guideline Q7 on good manufacturing practice for active pharmaceutical ingredients will come into effect on 4 February 2016 ([EMA/CHMP/ICH/468930/2015](#)).

Quality guidance

A draft guideline on the manufacture of the finished dosage form was released for public consultation until 9 January 2016 ([EMA/CHMP/QWP/245074/2015](#)). It provides clarification on the type of information that should be included in CTD Module 3 of marketing authorisation application dossiers with respect to the description of manufacturing process.



A draft guideline on residual solvents was released for public consultation until 9 January 2016 ([EMA/CHMP/ICH/82260/2006](#)). It provides revised recommendations on the classification of trimethylamine and methylisobutylketone in the 'ICH Impurities: Residual Solvents Guideline'.

The European Commission has released a draft guideline on Real Time Release Testing (RTRT) for consultation until 11 December 2015 ([Link](#)). It outlines the requirements for application of a RTRT approach in manufacturing. The main aim of the changes is to incorporate the application of RTRT to any stage in the manufacturing process and to any type of finished products, active substances and intermediates.

A reflection paper on the use of cocrystals of active substances in medicinal products has recently been adopted by the CHMP and the CVMP ([EMA/CHMP/CVMP/QWP/284008/2015](#)). It reflects the current thinking of the Committees on different aspects concerning the use of cocrystals of active substances in medicinal products, for human or veterinary use.

Non-Clinical and Clinical guidance

A revised guideline on the non-clinical and clinical requirements for a similar biological medicinal products containing biotechnology-derived proteins as active substances entered into force on 1 July 2015 ([EMA/CHMP/BMWP/42832/2005 Rev1](#)). It was updated on topics including: stepwise approach for the design of (non)clinical studies, use of pharmacodynamic markers, study design, populations, surrogate and clinical endpoints in efficacy trials, clinical safety and risk management plan.



A revised guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) will come into effect on 1 February 2016 ([EMA/CHMP/BPWP/410415/2011 rev 1](#)). It describes the marketing authorisation requirements for such products including biological data, pharmacokinetics, clinical trials and patient follow-up. The document was updated to ensure consistency with the guideline for human normal immunoglobulin for intravenous administration ([EMA/CHMP/BPWP/94033/2007 rev 2](#)).

A guideline on the clinical investigation of hepatitis B immunoglobulins will come into effect on 1 February 2016 ([EMA/CHMP/BPWP/585257/2009](#)). It sets out documentation to be included when an application is made for a marketing authorisation for a hepatitis B immunoglobulin. It covers biological data, pharmacokinetics, clinical trials and patient follow-up, and also includes guidance for authorised products where a significant change in the manufacturing process has been made.

A guideline on the development and evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing will come into effect on 1 January 2016 ([EMA/CHMP/336243/2013](#)).

A draft guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products has been released for consultation until 31 March 2016 ([EMA/CHMP/594085/2015](#)). The aim of this guideline is to outline the regulatory expectations for application dossiers and reflects both the scientific advances and the regulatory experience in the field of pharmacometrics that have implications for antimicrobial agents development programmes.

A draft guideline on the application of the principles of the ICH M7 guideline to calculation of compound-specific acceptable intakes has been released for public consultation until 3 February 2016 ([EMA/CHMP/ICH/458894/2015](#)). It discusses the derivation of acceptable intakes for mutagenic impurities with positive carcinogenicity data.

Product-specific guidance on bioequivalence studies for [capecitabine](#) will come into effect on 1 December 2015.

Other product-specific guidance on bioequivalence studies have been released for consultation until 1 November 2015

for four active substances: [zonisamide](#), [sitagliptin](#), [prasugrel](#) and [arsenapine](#).

A revised Questions & Answers document on positions on specific questions addressed to the Pharmacokinetics Working Party has been adopted ([EMA/618604/2008 Rev. 12](#)). It addresses specific questions in relation to pharmacokinetic evaluations and particularly the requirements and assessment of bioequivalence studies.

Regulatory and procedural guidance

A module compiling the regulatory and procedural requirements for the different types of influenza vaccines has been adopted on 22 May 2015 ([EMA/56793/2014](#)). It details the procedural aspects related to the submission of centralised marketing authorisation applications for influenza vaccines and subsequent updates of vaccine composition.

The EMA guidelines on accelerated assessment and conditional marketing authorisation, two key tools in the European legislation to accelerate patients' access to medicines that address unmet medical needs are being revised. Consultation has closed. Finalised guidance is expected in 2016. For details on the changes included in the proposed revisions of the guideline, please refer to the [Link](#).

Revised implementing rules on fees payable to the Agency came into force on 1 August 2015. The changes include the revision of definition for "distinct" good-clinical-practice (GCP) inspections and the extension of fee reductions for pharmacovigilance-related variations to marketing authorizations to veterinary medicines. Further details are available in the updated [Explanatory note on fees payable to the Agency](#).



Guidance describing the method used by the EMA to determine the number of “chargeable units” applicable to marketing authorisation holder for the purpose of fees for pharmacovigilance activities has been published ([EMA/409768/2015](#)).

The following EMA Q&A were recently updated:

- Pre-authorisation pre-submission guidance ([EMA/339324/2007](#)) (on e.g. EU RMP submission, timetable for evaluation, information to be provided on GCP inspections and GLP compliance, pre-approval GCP and GMP inspections, submission contact point, validation of dossiers);
- Similar biological product applications ([EMA/940451/2011](#)) and generic/hybrid applications ([EMA/CHMP/225411/2006](#)) (on e.g. information to be provided on GCP inspections and GLP compliance).

Electronic application form, Common repository

The use of the Electronic Application Form (eAF) is mandatory for all human and veterinary *centralised* procedures from 1 July 2015. Use of the eAFs will be compulsory for all EU procedures (centralised procedure, decentralised procedure, mutual recognition procedure and national procedure) as of January 2016 and the application forms in Word format will no longer be available from this date. Further details and guidance are available in a [user guide](#), a [technical guide](#), a [Questions & Answers](#) document, and on the [eAF website](#).

From 1 July 2015, companies should send *centralised* human applications to the European Medicines Agency’s (EMA) via the eSubmission Gateway/Web Client only. The dossiers should no longer be sent to individual Member States on CDs/DVDs or via the Common European Submission Platform (CESP). These applications will automatically be made available to all national competent authorities via a common online repository. For further information, please see the [esubmission website](#).

Review of the class waiver list

A revised list of class waivers for medicines that are not required to submit a paediatric investigation plan (PIP) will come into effect in 2018. The PDCO has revoked eight class waivers, updated fifteen class waivers and confirmed nine class waivers. Further information is available under [Link](#) and a [Questions & Answers](#) document.

Guidance for veterinary medicines

A revised 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 will come into force in March 2016 ([EMA/CVMP/IWP/205351/2006-Rev.1](#)). The objective of the revision is to remove the provision for an *in vivo* test, with a view to ensuring best practices with regard to implementation of 3Rs (replacement, reduction and refinement) principles.



A guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products will come into force on 1 April 2016 ([EMA/CVMP/ERA/52740/2012](#)). It provides guidance on how PBT/vPvB substances are screened and assessed in accordance Regulation (EC) No 1907/2006 (Registration, Evaluation, Authorisation and Restriction of Chemicals “REACH” regulation) and its guideline documents (ECHA 2014a-d).

A VICH guideline GL52 on bioequivalence: blood-level bioequivalence study will come into force in August 2016 ([EMA/CVMP/VICH/751935/2013](#)). It harmonised the data requirements associated with *in vivo* blood level bioequivalence for veterinary pharmaceutical products.

A draft guideline on the requirements for the production and control of immunological veterinary medicinal products was released for consultation until 31 January 2016 ([EMA/CVMP/IWP/206555/2010-Rev.1](#)). It was revised to include a new annex on the approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products for mammalian species and finfish.

A draft reflection paper on methods for demonstrating freedom from extraneous agents of the seeds used for the production of immunological veterinary medicinal products has been released for consultation until 31 January 2016 ([EMA/CVMP/IWP/251741/2015](#)).

Workshops, meetings and reports

The EMA is organising a workshop entitled **“Demonstrating significant benefit of orphan medicines concepts, methodology, and impact on access”** on 7 December 2015.

The aim of the workshop is to discuss the approach that should be followed by medicines developers to demonstrate the significant benefit of an orphan medicine over existing treatments. The deadline to register is 31 October 2015.

Further information about the program and details on registration can be found [here](#).



Reports, presentations and/or videos of the following meetings have been published:

March 2015

- Collaboration on neonatal issues between researchers and the European Medicines Agency ([Link](#))

May 2015

- European Medicines Agency-industry stakeholders platform meeting on paediatric medicines ([Link](#)).
- European Medicines Agency and European Network for Health Technology Assessment (EUnetHTA) ([Link](#))

June 2015

- European Union International Organization for Standardization (ISO) identification of medicinal products Task Force meeting ([Link](#)).
- Joint European Medicines Agency/Drug Information Association information day on International Organization for

Standardization identification of medicinal products standards: achieving compliance ([Link](#))

- European Medicines Agency workshop on the development of new medicinal products for the treatment of ulcerative colitis and Crohn’s disease ([Link](#)).
- Workshop on the therapeutic use of bacteriophages ([Link](#)).

July 2015

- Workshop on haemophilia registries ([Link](#)).

News from other organisations

European Consortium for Translational Medicine (EATRIS)

The European Consortium for Translational Medicine (EATRIS) is a non-profit organization that supports translational research across the EU. It is open to researchers and companies in need of support for advancing their biomedical innovations. Further information can be found on www.eatris.eu.



Orphan drugs support in Japan

The National Institute of Biomedical Innovation (NIBIO) provides guidance on its support programme for orphan drug and orphan medical device research and development promotion program, including dedicated support for SMEs (<http://www.nibio.go.jp/shinko/orphan/english/index.html>).

Registered SMEs

Currently, 1453 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.



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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