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# SME Office NEWSLETTER

Information for SMEs on the EU regulatory environment for medicines.
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## SME user guide

The user guide (Link) for SMEs operating in the pharmaceutical sector has been updated. The guide aims to support SMEs to better understand the EU legislative framework for medicines and the requirements for the development and authorisation of medicines for human or veterinary use. It provides an overview of data requirements to support a marketing authorisation, as well as the regulatory tools available to facilitate medicines' development.

## Medicines development for rare diseases

EMA and FDA have set up a new cluster on rare diseases to share experience and best practices on regulatory approaches to the development of medicines for rare diseases including topics such as:

- the design of clinical trials in small populations and the use of statistical analysis methods;
- the selection and validation of trial endpoints;
- preclinical evidence to support development programmes;
- the design of post-marketing studies, in particular in the context of early access mechanisms such as EMA's conditional marketing authorisation and FDA's accelerated approval;
- risk management strategies for long-term safety issues with medicines for rare diseases.

The cluster will meet once a month via teleconference and will be chaired jointly by FDA and EMA. Further information can be found in this document (EMA/633705/2016) and under this Link.

## Adaptive pathways

A report on the experience gained during the pilot project on adaptive pathways launched in March 2014 has been published on the EMA website (EMA/276376/2016). It highlights that adaptive pathways approach can bring multiple stakeholders together (regulators, health technology assessment bodies, healthcare professionals and patients) to agree on a prospective plan to generate data on a medicine across its lifespan in areas of unmet medical need. Companies interested in discussing such approach should refer to the guidance document (EMA/527726/2016). Enhanced support is provided to SMEs through additional pre-submission meetings. EMA is organising a workshop on 8 December 2016 to gather stakeholders' feedback on the adaptive pathways approach (Link).

# Non-clinical and clinical guidance

### New web layout for scientific guidelines.

For each guideline available on the EMA website, information is now displayed on a single page that shows the current version of the guideline with its full history including any drafts, reflection papers, concept papers and previous versions, and provides links to related content.

### Clinical Guidance.

A guideline on the use of pharmacokinetics and pharmacodynamics (PK-PD) in the development of antimicrobial medicinal products will come into effect on 1 February 2017 (EMA/CHMP/594085/2015). It provides guidance on the use of PK-PD analyses to define dose regimens for systemically active antibacterial agents, antimycobacterial agents and antifungal agents. It applies to initial clinical development programmes for new antimicrobial agents and those intended to support additional indications involving different pathogens or the use in special populations that may require alternative dose regimens.

A draft ICH guideline on general principles for the planning and design of multi-regional clinical trials has been released for consultation until 28 January 2017 (EMA/CHMP/ICH/453276/2016). Its aim is to increase the acceptability of such studies in regulatory submissions.

Draft revised guidance on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006 Rev. 1) and Crohn's disease (CPMP/EWP/2284/99 Rev. 2) have been released for consultation until 31 January 2017. These documents have been revised to provide an update on the design of studies in adult patients, including aspects relating to endpoints, comparators and potential claims. The revisions also provide further guidance on paediatric drug development for each indication.

A revised draft addendum to the guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections has been released for consultation until 31 January 2017 (EMA/CHMP/EWP/14377/2008 Rev 1). It addresses the clinical development of new agents to treat diseases due to Mycobacterium tuberculosis taking into account the development of new regimens to treat tuberculosis. It also clarifies the regulatory requirements with regards to data that should be generated to support the approval of new medicines or combinations of medicines.

A revised draft guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation has been released for consultation until 31 January 2017 (EMA/CHMP/458101/2016). It supports the use of innovative modelling and simulation approaches that are currently being used during the development of medicines. It describes the expected content of PBPK modelling and simulation reports included in applications for authorisation of medicinal products, paediatric investigation plans or clinical trial applications. An EMA workshop to gather stakeholders' feedback on the draft guideline will take place on 21 November 2016 and will be broadcast live (Link).

### Non-Clinical Guidance.

The CHMP guideline on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95) has been withdrawn, and companies should now refer to the WHO guideline on nonclinical evaluation of vaccines (Link). A questions and answers document has been published to provide clarification on the grounds for this decision and its impact for companies (EMA/CHMP/SWP/242917/2016).

A report on actions taken with regards to the review and update of EMA guidelines to implement best practices with regards to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products has been published on the EMA website (EMA/CHMP/CVMP/JEG-3Rs/677407/2015).

A draft CHMP/CVMP guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs (Replacement, Reduction and Refinement) has been released for consultation until 31 January 2017 (EMA/CHMP/CVMP/JEG-3Rs/94436/2014).

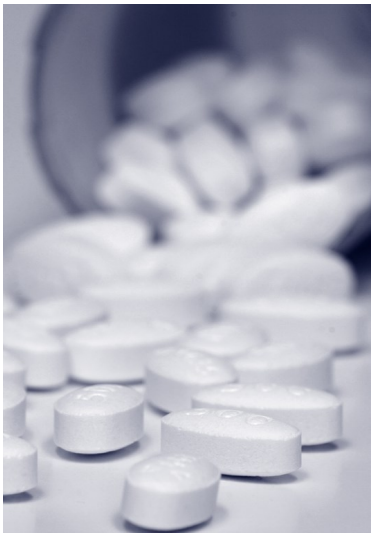
A draft questions and answers document on the ICH guideline (S9) on the non-clinical evaluation for anticancer pharmaceuticals has been released for consultation until 28 January 2017 (EMA/CHMP/ICH/453684/2016). It facilitates the implementation of the guideline with a view to continuing progress with the implementation of the 3Rs of Reduction, Refinement, and Replacement in the use of animals.

The non-clinical and clinical modules of the guideline on influenza vaccines will come into effect on 1 February 2017 (EMA/CHMP/VWP/457259/2014). The new guidance takes into account the current understanding of the predictive value of non-clinical studies for clinical situations and knowledge that individual types of influenza vaccines may differ from each other in terms of their immunogenicity, efficacy and safety. It also reflects lessons learned from the influenza A(H1N1) pandemic and experience acquired from scientific advice and marketing authorisation applications. Two other separate modules of this guideline cover the quality and regulatory requirements for new influenza vaccines (EMA/CHMP/BWP/310834/2012; EMA/56793/2014).

# Quality guidance

An ICH guideline (Q3D) on elemental impurities came into effect in June 2016 for new marketing authorisation applications, and will enter into force in December 2017 for authorised medicines (EMA/CHMP/ICH/353369/2013). It describes a process to assess and control elemental impurities in the finished product using the principles of risk management as described in ICH Q9.

The following guidelines have been revised to reflect current best practices with regards to implementation of 3Rs approaches and came into effect in September 2016:



- A guideline laying down quality requirements (development, production, characterisation and specifications) for monoclonal antibodies and related products in the context of a marketing authorisation application (EMA/CHMP/BWP/532517/2008).
- A guideline providing guidance on specific requirements related to the development and validation of potency assays for cell-based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/271475/2006 rev.1).
- A guideline on production and quality control of animal immunoglobulins and immunosera for human use (EMA/CHMP/BWP/3354/1999 rev.1)

**The following questions and answers documents have also been updated:**

- Part 1 of the questions and answers on quality of medicines (updated section on active substance master file procedure) (Link);
- Questions and answers on Good Manufacturing Practices (new section on data integrity) (Link).

# Veterinary medicines

Updated advice on the use of colistin products in animals and the development of resistance and possible impact on human and animal health in the EU has been adopted by CVMP and CHMP in July 2016 (EMA/CVMP/CHMP/231573/2016). It provides an analysis of colistin toxicity, susceptibility testing, activity and resistance mechanisms, risk profile and risk management options, and was updated in response to the discovery of a new bacterial mechanism of resistance to colistin. EMA recommends that colistin-containing medicines should only be used as a second line treatment in animals and that their sales should be minimised across the EU to reduce the risk of antimicrobial resistance. Further information can be found under this link.

A revised guideline on testing and evaluation of the efficacy of veterinary antiparasitic products intended for the treatment and prevention of tick and flea infestations in dogs and cats will come into effect on 1 February 2017 (EMEA/CVMP/EWP/005/2000-Rev.3).

A draft guideline on the higher-tier testing of veterinary medicinal products to dung fauna was released for consultation until 31 January 2017 (EMA/CVMP/ERA/409350/2010). It provides guidance on how to investigate the environmental effects of veterinary medicinal products containing antiparasitic substances in higher tier laboratory tests and field studies, in situations where a risk to dung flies or beetles is indicated.

A revised draft guideline on the harmonisation of withdrawal periods has been released for consultation until 31 January 2017 (EMA/CVMP/SWP/735325/2012). The approach used for considering residues present at levels below the limit of quantification (LOQ) has been revised.

**The following questions and answers document have been updated**:

- Questions and answers on the implementation of the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of VICH guidelines GL6 (phase I) and GL38 (phase II) (EMEA/CVMP/ERA/172074/2008 Rev. 5);
- Questions and answers on mentioning solvents in the product information of veterinary medicinal products authorised via the centralised procedure (EMA/CVMP/550607/2015).

# Regulatory and procedural guidance

## Medicinal products for human use

A revised guideline on the processing of renewals in the centralised procedure will enter into force on 1 November 2016 (EMEA/CHMP/2990/00 Rev.5). It clarifies the CHMP and PRAC rapporteurs/co-rapporteurs involvement in the renewal process. It also specifies that, to facilitate the assessment of the addendum to clinical overview, new signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be highlighted in the data provided.

The following documents were updated accordingly:

- EMA post-authorisation procedural advice for users of the centralised procedure (on renewal of MAA but also annual re-assessment of a marketing authorisation application (MAA), renewal of MAA, annual renewal of conditional marketing authorisation, transparency) (EMEA-H-19984/03 Rev. 64);
- Pre-submission checklist for 5-year renewal application (EMA/190616/2016).

**The following guidance documents and checklists were also updated:**

- EMA pre-authorisation procedural advice for users of the centralised procedure (on submission of ASMFs) (EMA/339324/2007 Cor.1);
- Pre-submission checklist for annual renewal of conditional marketing authorisation applications (EMA/198337/2016);
- Pre-submission checklist for annual re-assessment of a marketing authorisation application under exceptional circumstances (EMA/199522/2016).

## Veterinary medicinal products

A questions and answers document on how to express the frequency of adverse reactions in the product information has been published on the EMA website (EMA/CVMP/150343/2016). It provides advice on the wording of section 4.6 of the Summary of Product Characteristics (SPC) and section 6 of the Package Leaflet in line with the convention of frequency groupings for adverse reactions that is included in the veterinary Quality of Review Document template.

**The following procedural guidelines have also been updated:**

- Guidance for companies requesting classification as minor uses minor species/limited markets (EMA/CVMP/370663/2009 – Rev.2);
- Guidance for companies requesting scientific advice (EMEA/CVMP/172329/2004-Rev. 4) and corresponding template of letter of intent for request of scientific advice (Link).

# Pharmacovigilance for human medicines

## Report on implementation of pharmacovigilance legislation

A 3-year report on the pharmacovigilance activities of the European medicines regulatory network since the new pharmacovigilance legislation came into effect in July 2012 has been published by the European Commission (Link to the report, Link to the EC webpage). It highlights that closer collaboration between EMA, the European Commission and EU Member States has enhanced the monitoring of the safety of human medicines throughout their life cycle, for the benefit of patients.

## Guidance on pharmacovigilance for human medicines

A new chapter on good pharmacovigilance practices providing guidance on how to better monitor and manage the safety of biological medicines came into effect on 16 August 2016 (EMA/168402/2014). It applies to biological medicines, biosimilars and medicines which contain the same or a closely related active substance but are not authorised as biosimilars.

A revised good pharmacovigilance practices guideline on Post-authorisation safety studies (PASS) came into effect on 9 August 2016 (EMA/813938/2011 Rev 2*). The update clarifies the link between the legislation on non-interventional PASS and the corresponding updated addendum providing additional information on legal requirements and recommendations for the submission of information on non-interventional PASS (EMA/395730/2012 Rev 2*).

An 'Important Medical Event Terms' (IME) list aiming at facilitating the classification of suspected adverse reactions as well as aggregated data analysis and case assessment in the day-to-day pharmacovigilance activities of stakeholders in the EU has been published on the EMA website (EMA/154648/2016).

**The following questions and answers document have also been updated:**

- Questions and answers documents on data elements for transmission of individual case safety reports (EMA/CHMP/ICH/3943/2003);
- Questions and answers document on signal management (EMA/261758/2013 Rev 2- Corr 1*)

# Reports, workshops and meetings

## Selection of upcoming events

### November 2016

- Identifying opportunities for 'Big data' in medicines development and regulatory science– 14 & 15/11/2016 (Link)
- Committee for Advanced Therapies (CAT) workshop: scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products -15 & 16/11/2016 (Link to the event, Link to the press release)
- EMA workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation - 21/11/2016 (Link)

### December 2016

- Adaptive pathways workshop – 08/12/2016 (Link)
- EMA /European Biopharmaceutical Enterprises (EBE) fifth annual regulatory conference on optimising the development of advanced therapies to meet patient needs – 16/12/2016 (Link)

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

- Report of workshop (07/12/2015) - Demonstrating significant benefit of orphan medicines: concepts, methodology and impact on access – (EMA/6690/2016)
- Report - Highlights from the EMA industry platform meeting held on 21 April 2016 on the operation of the centralised procedure for human medicinal products (EMA/526723/2016)
- Report of workshop (30/06/2016) on single-arm trials in oncology (Link)
- EU International Organisation for Standardisation (ISO) identification of medical products (IDMP) task force meetings (30/06 and 01/07/2016) (Link)
- Eighth industry stakeholder platform: operation of the EU pharmacovigilance legislation (01/07/2016) (Link)
- Implementation of the ISO IDMP standard: introduction to SPOR data services (04/08/2016) (Link)

# News from other organisations

A fact sheet on funds for the health sector in Europe has been published by the European Commission (Link). It gives an overview on its investment plan to mobilise funds for new technologies, innovative products and medical research.

The EU SME Centre is a European Union initiative that provides a comprehensive range of support services to European SMEs getting them ready to do business in China. Advice and support can be provided in a series of areas including business development, standards and human resources. Further information can be found under Link.

# Registered SMEs

Currently, 1738 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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