45 Issue 45
November 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SME Office NEWSLETTER

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

An agency of the European Union

IN THIS ISSUE

Advanced Therapy Medicinal Products

The guideline on quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) will come into effect on 13 January 2019. It revises extensively the note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) to take into account legislative requirements. Guidance for viral vectored vaccines (CHMP/VWP/141697/2009) and genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev. 1; open for public consultation until 31 July 2019) are included in separate documents.

A report on the expert meeting on genome editing technologies used in medicine development held at EMA on 18/10/2017 has been published (Link).

Orphan and paediatric medicines

A European Commission (EC) public consultation on the impact of the EU legislation in supporting the development of pediatric medicines for rare diseases was launched on 12 October 2018. The consultation seeks to gather feedback from stakeholders on the role of the orphan regulation in the development of and access to orphan medicines (Link). The deadline for comments is 4 January 2019.

EMA and EC have published a joint action plan to support the development of medicines for children in Europe (Link). It addresses the challenges identified by the EC's ten-year report on the implementation of the paediatric legislation (Link) and takes into account feedback received during a multi-stakeholder workshop, which took place in March 2018 (Link). More information is available on the EMA website (Link).

Medicines' availability

The HMA/EMA taskforce on availability of authorised medicines for human and veterinary use has published its work programme for the next two years (Link). It lists actions for regulators and industry to ensure the availability of medicines for the benefit of patients in the EU. In addition, the taskforce has published a reflection paper on the availability of authorised medicines for

human and veterinary use (Link) which provides an oversight of existing initiatives and proposes actions to facilitate better prevention, identification, management and communication of shortages (see also stakeholders meetings on 8 November 2018 (Link) and 9 November 2018 (Link)).

Good Manufacturing Practice

Falsified medicines directive

A letter to stakeholders on the falsified medicines directive has been published (Link). It outlines the obligations of marketing authorisation holders, manufacturers and other suppliers of medicines, and serves as a reminder of the February 2019 deadline for the implementation of safety features (unique identifier and anti-tampering devices for prescription medicines). More information is available on the EC (Link), HMA (Link) and EMA (Link) websites.

Extension of mutual recognition agreements

The mutual recognition agreement between the EU and Japan has been extended to include sterile medicines, certain biological medicines including vaccines and immunologicals, and active pharmaceutical ingredients (APIs) of medicines covered in the agreement (Link).

The implementation of the mutual recognition agreement between the EU and US continues to progress with FDA confirming the capability of Portugal to carry out GMP inspections at a level equivalent to the US (Link).

Scientific guidelines

Quality guidelines

An ICH guideline M9 on biopharmaceutics classification system based biowaivers (EMA/CHMP/ICH/493213/2018) is open for consultation until 31 July 2019. It provides guidance on exemptions for *in vivo* bioequivalence studies where assumptions of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Bio-waivers may be used to demonstrate bioequivalence e.g. between products used in early clinical development and commercialisation, line extensions of the same pharmaceutical form of innovator products, in generics applications, and to support post-approval changes that would otherwise require in vivo bioequivalence evaluation.

Clinical guidelines

A guideline on good pharmacogenomic practices (EMA/CHMP/718998/2016) came into effect on 1 September 2018. It provides recommendations for the conduct of genomic studies to provide high quality information on the impact of genomic variability on drug response.

A guideline on the clinical investigation of products for the treatment of axial spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*) came into effect on 1 May 2018. It was revised to reflect changes in clinical practice, include patients with non-radiographic axial spondylitis, as well as review treatment goals, outcome measures and the design of confirmatory trials.

The following guidelines will come into effect on 1 January 2019. They have been revised to provide updated guidance on the design of studies in adult patients, primary and secondary endpoints, comparators and paediatric data requirements, including data extrapolation from adults:

- Guideline on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006 Rev.1).
- Guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 2).

A draft guideline on the clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.3) is open for consultation until 17 February 2019. It was revised to include the new classifications and definitions of seizure types and epilepsies, the acceptance of add-on studies in support of a monotherapy claim on a case-by-case basis, new sections on neonates and status epilepticus, and changes related to paediatric developments.

A draft questions and answers document on Data Monitoring Committee (DMC) issues (EMA/492010/2018) has been released for consultation until 31 July 2019. It complements the CHMP 'Data Monitoring Committee' guideline (EMEA/CHMP/EWP/5872/03) and provides clarifications on the roles and responsibilities of DMC in the product lifecycle.

Pharmacovigilance

Pharmacovigilance in the paediatric population

A new EMA/HMA GVP chapter on specific considerations for pharmacovigilance in the paediatric population (EMA/572054/2016) came into effect on 8 November 2018. It integrates paediatric pharmacovigilance within the overall EU pharmacovigilance. Guidance is provided on how to make best use of pharmacovigilance tools and processes to address the needs of the paediatric population, and how requirements should be adapted (see also updated GVP introductory cover note (EMA/722239/2018)).

Revised pharmacovigilance fees

Revised pharmacovigilance fees accounting for inflation (1.7%) came into effect on 18 October 2018 (Link). The explanatory note on pharmacovigilance fees payable to the Agency has been updated accordingly (Link).

EudraVigilance

EMA has integrated the services of EudraVigilance with EMA's Account Management portal and Organisation Management Service (OMS) and all users (including organisations) now need an active EMA account created through the EMA Account Management portal. EMA has published a registration manual (Link) and updated its EudraVigilance registration webpage (Link) with new information on how to register, access or manage their account for EudraVigilance (human) production environment. The EudraVigilance stakeholder questions and answers document (EMA/390861/2018) has been updated to reflect these changes. An interactive guide on EudraVigilance registration has also been published (Link).

Other new or updated EudraVigilance documents include:

- Updated EudraVigilance release notes (Link);
- Updated EudraVigilance training material (Link);
- Updated guidance regarding the electronic submission of Article 57 data (Link);
- Updated important medical event terms list (IME-List) (Link);
- Guidance on inclusion/exclusion criteria of the IME-List (EMA/617687/2018).

Regulatory guidance

The following guidance has been updated:

- Pre-authorisation guidance (EMA/821278/2015) (e.g. on change of applicant in an ongoing application and pre-submission meetings);
- Post-authorisation guidance (EMEA-H-19984/03 Rev. 8) (e.g. on type II variations, submission of revised product information, extension applications, post-authorisations measures submission and change of contact person in application form);
- QRD general principles regarding the summary of product characteristics (SmPC) information for a generic/hybrid/biosimilar product (EMA/627621/2011 rev.1) (e.g. on information to be included in sections 4.1 and 4.2 of the SmPC);
- Dossier requirements for nationally authorised products (referrals, post-authorisation safety studies '107', work-sharing, signal detection procedures) and ancillary medicinal substances in a medical device (EMA/13015/2014 Rev. 7);
- Questions and answers on Article 31 non-pharmacovigilance referrals (EMA/457344/2016 Rev. 2) (e.g. on submission of responses).

Substance, product, organisation and referential (SPOR)

The document 'On-boarding of users to SPOR data services' has been updated (Link). It provides detailed guidance for stakeholders on the implementation of the SPOR programme and using RMS and OMS data management services. The guidance applies to both human and veterinary stakeholders with different implementation timelines depending on business processes (e.g. eAF, IRIS portal, EV-user registration).

Veterinary medicines

New legislation for veterinary medicines

The European Parliament has adopted the final texts of the new veterinary medicines regulation (Link) and the corresponding update of Regulation 726/2004. The new regulation aims to increase the availability of veterinary medicines, reduce administrative burden, stimulate competitiveness and innovation in the veterinary sector, improve the functioning of the internal market and address the public health risk of antimicrobial resistance. The regulation is a new standalone set of rules covering all aspects of veterinary medicines (at national and centralised level) that will replace Directive 2001/82 and the veterinary product-specific articles of Regulation 726/2004. The new regulation will become applicable by the end of 2021.

Veterinary Pharmacovigilance

Updated guidance on the use of the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) have been published (Link).

The following questions and answers documents have been updated:

- Adverse event reporting (EMA/CVMP/PhVWP/145186/2013-Rev.3) (e.g. classification of adverse events within target species subgroups and off-label use);
- Preparation, management and assessment of periodic safety update reports (PSURs) (EMA/CVMP/PhVWP/126661/2009-Rev.4-corr) (e.g. abridged PSURs, medication errors not associated with adverse events, additional electronic line listings, incidence calculations and product information).

Antimicrobial guidance

A reflection paper on 'The use of aminopenicillins and their beta-lactamase inhibitor combinations in animals in the European Union: development of resistance and impact on human and animal health' is open for public consultation until 21 December 2018 (EMA/CVMP/AWP/842786/2015). It reviews the available information on the use of aminopenicillins and beta-lactamase inhibitor combinations in veterinary medicines in the EU, their effect on the emergence of antimicrobial resistance and the potential impact of resistance on human and animal health.

The public consultation on the draft guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/383441/2005-Rev.1) has been extended until 31 August 2019.

Maximum Residue Limits (MRLs)

The following guidelines have been published:

- A VICH guideline on 'Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods' (EMA/CVMP/VICH/176637/2014); effective from June 2019;

- A guideline on 'Determination of withdrawal periods for edible tissues of food producing animals' (EMA/CVMP/SWP/735325/2012) replacing EMEA/CVMP/036/95); effective from April 2019.

Quality guidelines

A draft VICH guideline on stability testing of new veterinary drug substances and medicinal products in climatic zones III (hot and dry) and IV (hot and humid) (EMA/CVMP/

VICH/335918/2016) is open for public consultation until 31 December 2018.

Clinical guidelines

A draft guideline on data requirements for veterinary medicines for the prevention of transmission of vector- borne diseases in dogs and cats (EMA/CVMP/EWP/278031/2015) is open for public consultation until 31 August 2019.

Regulatory science strategy to 2025

The 'Regulatory Science Strategy to 2025' is a proposed new high-level plan for advancing the EMA's engagement with regulatory science by identifying key areas where new or enhanced engagement of the network is essential and where advances in regulatory science will need to be adopted. It will help to shape the vision for the next EU Medicines Agencies Network Strategy (2020–2025). A workshop was held at EMA on 24/10/2018 to gather insight from stakeholders on the key areas in human medicines to be covered (Link) and a workshop to discuss veterinary medicines will take place at EMA on 06/12/2018. More information can be found on the EMA website (Link).

United Kingdom's withdrawal from the European Union ("Brexit")

The EMA's Brexit preparedness business continuity plan entered its third phase on 1 October 2018 (Link). EMA will focus its activities on core business activities during its move to the Netherlands. Guideline development and revision will be reduced and activities of non-product related working parties put on hold. Pre-submission meetings for human and veterinary centralised initial applications will be held remotely until the end of 2019. In addition, as of 1 August 2018 EMA has suspended all new activities related to clinical data publication as a result of business continuity plans. No new data packages will be processed until further notice. Further details are available in the implementation plan (Link).

In April 2018, the EU-27 Member states and EMA completed the redistribution of the UK's portfolio of centrally authorised products to (co)-rapporteurs and informed marketing authorisation holders. EMA has now published the cut-off date for UK (co)-rapporteur appointments for pre- and post-authorisation activities (e.g. PRIME, scientific advice, orphan designation or variations) based on the timelines from submission to outcome (Link).

Presentations and a report from the industry stakeholder meeting on Brexit and the operation of the centralised procedure for human and veterinary medicines, which took place on 24 September 2018, have been published (Link).

Further information on can be found in the dedicated Brexit (Link) and relocation to Amsterdam webpages (Link). SMEs can address questions relating to Brexit directly to SME@ema.europa.eu.

Reports, presentations, videos and future events

Reports of interest:

- Report on Clinical data publication (Policy 70) (Link)
- EMA interaction with industry stakeholders - Annual report 2017 (Link)
- Annual report of the European network of paediatric research at the European Medicines Agency (Enpr-EMA) Report of Coordinating Group and networks meeting (Link); 2018 Annual workshop of Enpr-EMA (Link).

Presentations and reports of the following events have been published:

- 14th industry stakeholder platform - Operation of European Union pharmacovigilance- 28 September 2018 (Link)
- Third industry stakeholder platform on research and development support-18 May 2018 (Link)
- Workshop on the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development 3-4 May 2018 (Link)

Future events of interest:

- Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies) 26/11/2018 (Link)
- EMA/HMA/EC workshop on electronic product information (ePI) 28/11/2018 (Link)
- Innovation and biomarkers in cancer drug development (IBCD) 2018 29/11/2018 -30/11/2018 (Link)

Registered SMEs

Currently, 1875 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 Applying for SME status 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 their regulatory strategy;
- organising info days 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: sme@ema.europa.eu
Tel: +44 (0)20 3660 8787

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact