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EUROPEAN MEDICINES AGENCY
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# SME Office NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
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# Support to early access to medicines

## Launch of the PRIority Medicines (PRIME) scheme

The EMA has launched the PRIME scheme to strengthen the support to development of medicines that target an unmet medical need and to facilitate their access.

It focuses on medicines that may offer a major therapeutic advantage over existing treatments or benefit patients with no treatment options and is limited to products under development yet to be placed on the EU market. Eligible products will benefit from an enhanced support to optimise the generation of robust data on a medicine's benefits and risks. It will also enable accelerated assessment of marketing authorisation applications.

PRIME is open to all companies on the basis of preliminary clinical evidence. SMEs and applicants from the academic sector can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

Further information is available on an EMA dedicated webpage (link) and in a press release. Queries can be directed to prime@ema.europa.eu.

## Accelerated assessment and conditional marketing authorisation

Revised guidelines on accelerated assessment of marketing authorisation applications and conditional marketing authorisation will enter into force on 1 June 2016. Requests for accelerated assessment of dossiers should be submitted 2-3 months prior to filing. Hence, the new timetables described in the guideline will apply to evaluations starting in September 2016.

The guideline on accelerated assessment (EMA/CHMP/671361/2015 Rev. 1) has been revised to provide further guidance on the rationale for major public health interest, in particular where comprehensive clinical data may not be available (e.g. conditional marketing authorisation). The revision also optimises the overall review timetable and emphasises the importance of an early dialogue and planning with the EMA. Question 11 of the pre-submission guidance has been updated to reflect this change (Link).

The guideline on conditional marketing authorisation (EMA/CHMP/509951/2006, Rev.1) has been revised to provide clarifications on the demonstration of unmet medical need and positive benefit-risk balance when less comprehensive data are available. Furthermore, it emphasizes the importance of prospective planning and early advice and dialogue during development.

Aspects relating to renewals of conditional marketing authorisations and compliance with specific obligations have also been developed.

Further details can be found in the following questions and answers (Link1; Link2).

The EMA has released a comprehensive web page detailing the EU early access regulatory tools for medicines addressing major public health needs (i.e. accelerated assessment, conditional marketing authorisation and compassionate use). It also includes an overview table of the development support tools to help sponsors identify when and how to use them (EMA/531801/2015).

### EMA parallel scientific advice with HTA bodies

A report on the Agency's pilot program of parallel scientific advice with health-technology-assessment (HTA) bodies has been published (EMA/695874/2015). Parallel scientific advice with HTA bodies allows medicines developers to receive simultaneous feedback on their development plans and is now routinely offered as part of the Agency's scientific advice activities. Procedural details are set out in a best practice guide (EMA/502692/2015) and more information is available on the EMA website (Link). This initiative is in line with the efforts between EMA and the European network for Health Technology Assessment (EUnetHTA) to foster cooperation between regulators and HTA bodies. Further information on the work of EUnetHTA can be found under this Link.

### Publication of clinical trial data (Policy 0070)

Guidance on the implementation of the EMA policy on the publication of clinical data for medicinal products for human use (EMA/90915/2016) has been finalised. The guidance document includes sections on procedural aspects, anonymisation of personal data and redaction of commercial confidential information. The first clinical trial reports are currently foreseen to be publicly available in September 2016.

The policy applies to clinical reports contained in all initial marketing-authorisation applications submitted on or after the policy's entry into force on 1 January 2015 and to applications submitted on or after 1 July 2015 to vary a marketing authorisation for an extension of indication or a line extension. In the initial phase of the policy's implementation, the EMA will contact the companies for which the decision-making process has been finalised since the policy entered into force, and will specify the deadline by which each company will have to provide the redacted documents for the product in question.

Later in 2016, the EMA will announce a webinar on the implementation of clinical data publication policy. Further information on Policy 0070 is available under this Link and in a dedicated press release (Link).

## Guidance on pharmacovigilance for human medicines

### Revision of Good Pharmacovigilance Practices

A revision of module V of the Good Pharmacovigilance Practices (GVP) on risk management system has been released for consultation until 31 May 2016 (EMA/838713/2011 Rev 2). It clarifies what a risk management plan should focus on and the expected changes in the risk management plan (RMP) during the life cycle of a product. It also updates the requirements for different types of initial marketing authorisation applications to create more risk-proportionate RMPs. The RMP template for initial marketing authorisation application undergoes public consultation in parallel. Further information is available in a dedicated press release (Link).

### Reliance on Article 57 database for key pharmacovigilance information

As of 1 February 2016, for both centrally and nationally authorised medicines, marketing-authorization holders should notify the Agency of administrative changes concerning the qualified person for pharmacovigilance (QPPV) and the location of the pharmacovigilance system master file (PSMF) through the Article 57 database only. These changes must be notified to the competent authorities immediately, and no later than 30 calendar days from the date the change applies. The submission of a type IAIN variation to EMA or NCAs is no longer required.

The questions and answers document on 'Electronic submission of Article 57(2) database' (EMA/159776/2013), the 'Chapter 3.II: Extended EudraVigilance product report message (XEVPRM) user' guidance document (EMA/135580/2012) and the legal notice on the implementation of Article 57(2) of Regulation (EC) 726/2004 (EMA/505633/2011, Rev. 2) have been updated to reflect this change.

### Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The results of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), a project aiming at developing innovative methods to improve and strengthen the monitoring of the benefits and risks of medicines marketed in the European Union, have been published (EMA/180815/2016). Further information can be found on the EMA website (Link).

# Non-Clinical and Clinical guidance

A revised guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products will come into effect on 1 May 2016 (EMA/CHMP/BPWP/144533/2009 rev.1). It covers the clinical investigations to be conducted, describes the documentation for marketing authorisation applications and provides guidance for authorised products where a significant change in the manufacturing process has been made. It was revised following the 2013 EMA/EDQM workshop on potency assays.

A revised guideline on the evaluation of the pharmacokinetics of products in patients with decreased renal function will come into effect on 1 July 2016 (EMA/CHMP/83874/2014). It provides recommendations on situations in which pharmacokinetic studies should be performed in subjects with decreased renal function and in patients on dialysis treatment. The revision includes advice on how to study the effect of reduced renal function on drugs that are primarily hepatically eliminated, recommendations to use an accurate method for determination of glomerular filtration rate in a pharmacokinetic study, and an absolute measure of renal function in the dosing recommendations for patients with impaired renal function.

A revised guideline on epidemiological data for blood transmissible infections (EMA/CHMP/BWP/548524/2008 rev 1; appendices (EMA/177105/2016 Rev.1)) will come into effect on 30 August 2016. It outlines the scientific data requirements for epidemiological data for applications to the EMA for Plasma Master File (PMF) certification, re-certification and variation. The revision provides additional guidance to PMF holders on e.g. residual risk calculations, monitoring period, approaches to identify trends in viral marker rates and epidemiological data requirements for approval of blood/ plasma collection centres and blood establishments.

A guideline on the clinical investigation of medicinal products for the treatment of venous thromboembolic (VTE) disease will come into effect on 1 September 2016 (EMA/CHMP/41230/2015). It replaces the previous note for guidance (CPMP/EWP/563/98) and includes updated sections on initial and extended treatment of VTE, clinical requirements for the treatment of deep and superficial vein thrombosis, use of alternative imaging techniques for diagnosis, controls in comparative trials and assessment of bleeding events.

A draft ICH guideline on genomic sampling and management of genomic data (E18) has been released for consultation until 31 May 2016 (EMA/CHMP/ICH/11623/2016). It will facilitate the implementation of genomic studies by enabling a common understanding of critical parameters for the collection, storage and optimal use of genomic samples and data. It also provides considerations regarding subject privacy, data protection, informed consent and transparency of findings.

A draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias has been released for consultation until 31 July 2016 (EMA/CHMP/539931/2014). It addresses the impact of new diagnostic criteria including early and asymptomatic disease stages on clinical trial design, the design of long-term efficacy and safety studies, the choice of outcome parameters and the use of biomarkers. Further information can be found under this Link.

A draft guideline on the clinical development of medicinal products for the treatment of autism spectrum disorder (ASD) was released for consultation until 31 August 2016 (EMA/CHMP/598082/2013). It provides guidance on the diagnostic criteria, definition of target treatment population, and efficacy and safety criteria for clinical trials. Further information can be found under this Link.


A draft guideline on the clinical investigation of products for the treatment of chronic heart failure has been released for consultation until 31 August 2016 (EMA/CHMP/392958/2015). It provides guidance to applicants on the development of medicinal products for the treatment of patients with chronic heart failure, including those in the post-acute phase of heart failure. The revisions relate to e.g. details on types of heart failure, patient populations, efficacy criteria and the need for morbidity and mortality trials.

A revised questions and answers document on the ICH guideline on the clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs (ICH E14) was updated to include clarifications on the use of concentration response modelling of QTc Data. (EMA/CHMP/ICH/310133/2008).

A revised draft guideline on the evaluation of anticancer medicinal products has been released for consultation until 15 September 2016 (EMA/CHMP/205/95 Rev.5). The revision simplifies the section on exploratory trials for cytotoxic compounds, elaborates on the importance of exploratory studies to identify the most appropriate target population with optimised benefit risk and expands on condition-specific guidance.

A regulatory notice on changes being considered to the guideline on rodent carcinogenicity testing of pharmaceuticals (ICH guideline S1) has been released for information (EMA/CHMP/ICH/536328/2013 Rev. 1). The goals of these potential changes are to introduce a more comprehensive and integrated approach to address the risk of human carcinogenicity of small molecule pharmaceuticals and to define conditions under which 2-year rat carcinogenicity studies add value to that assessment.

# Quality guidance

A reflection paper on the chemical structure and properties criteria for the evaluation of a 'new active substance' (NAS) status of chemical substances has been adopted by the CHMP (EMA/CHMP/QWP/104223/2015). It provides clarifications on the chemical structure and properties criteria to be taken into account to qualify a chemical active substance as NAS, as well as the elements that need to be substantiated in relation to a claim of considering an active substance as NAS.

# Regulatory and procedural guidance

### Introduction of safety features

Directive 2011/62/EU on falsified medicines for human use (Link) introduces harmonised safety and strengthened control measures across Europe by applying new safety measures.

A delegated act on safety features (Commission Delegated Regulation (EU) 2016/161) was published on 9 February 2016 and introduces two safety features: a unique identifier (a 2-dimension barcode) and an anti-tampering device, to be placed on the packaging of most medicines for human use. Marketing authorisation holders are required to place the safety features on the packaging of most prescription medicines and certain non-prescription medicines no later than 9 February 2019. The annexes of the regulation include the list of medicines subject

to the new requirement.

Further information, including the corresponding implementation plan (EMA/785582/2014 rev.1), is available on the EMA webpage on falsified medicines (Link). The EMA has also revised the product information templates for human medicines (Link) to enable the implementation of the new rules.

### Adjusted fees for applications to EMA

Adjusted fees for applications to EMA came into effect on 1 April 2016. Further information is available in the explanatory note on the fees payable to the Agency (Link) and on the EMA website (Link). Fees charged for pharmacovigilance procedures in accordance with Regulation (EU) 658/2014 will be updated in July 2016.

### The following guidance documents were updated:

- EMA pre-authorisation procedural advice for users of the centralised procedure (on e.g. conditional marketing authorisation, accelerated assessment procedure, pharmacovigilance system, submission date for eligibility requests) (EMA/339324/2007)
- EMA post-authorisation procedural advice for users of the centralised procedure (on e.g. type IA variation, type II variation, annual renewal of conditional marketing application, pharmacovigilance system, transfer of marketing authorisation) (EMEA-H-19984/03 Rev. 59)
- Questions and answers on the variations guidelines in the centralised procedure (on e.g. introduction of/or changes to the pharmacovigilance system) (EMA/427505/2013 Rev.3)
- Questions and answers on type II variations (Link) and on extension applications (Link).
- Guidance for sponsors on post-orphan medicinal product designation procedures (on e.g. inventory of orphan incentives in Member States) (EMA/62801/2015 Rev. 2).

# Guidance for veterinary medicines

A revised guideline on the data requirements for the demonstration of therapeutic efficacy for veterinary medicinal products containing antimicrobial substances will come into effect on 1 August 2016 (EMA/CVMP/627/2001-Rev.1).

A revised draft guideline on the conduct of efficacy studies for intramammary products for use in cattle has been released for consultation until 31 May 2016 (CVMP/344/1999-Rev.2). It provides guidance on the design, conduct and reporting of pre-clinical and clinical studies submitted in support of new marketing authorisation applications or to vary the conditions for use of an already authorised product. The revisions elaborate on aspects related to the treatment and prevention of (sub)clinical mastitis and infections.


Four revised guidelines relating to Minor Use or Minor Species (MUMS) have been released for public consultation until 31 July 2016. The documents were updated in light of the experience gained and clarify the applicability of the MUMS data requirements:

- Guideline on efficacy and target animal safety data requirements (EMA/CVMP/EWP/117899/2004–Rev.1);
- Guideline on quality data requirements (EMA/CVMP/QWP/128710/2004-Rev.1);
- Guideline on safety and residue data requirement (EMA/CVMP/SWP/66781/2005–Rev.1);
- Guideline on data requirements for immunological veterinary medicinal products (EMA/CVMP/IWP/123243/2006-Rev.3).

The annual report on the operation of the MUMS (minor use, minor species) / limited market policy providing information on the products classified under this policy and detailing the types of products for which support is provided has been published (EMA/57157/2016). The number of requests for classification under the policy remains consistent year-on-year with 28 in this reporting period (152 requests in total since start of policy in September 2009). The policy has been highly successful in terms of incentivising the submission of requests for classification of products as MUMS. These classifications are starting to result in newly authorised products becoming available for minor species and limited markets.

Two draft VICH guidelines on the criteria to waive target animal batch safety testing for inactivated vaccines (EMA/CVMP/VICH/582610/2009) and for live vaccines (EMA/CVMP/

VICH/313610/2013) have been released for consultation until 1 August 2016.

Two CVMP papers on the development of veterinary medicines based on stem cells and monoclonal antibodies were released for consultation until 15 May 2016. The finalised documents may lead to the development of future guidance for these products:

- Monoclonal antibodies for veterinary use: specific questions to be addressed by Ad Hoc Group on Veterinary Novel Therapies (ADVENT) (EMA/CVMP/ADVENT/276476/2015)
- Stem cell-based products for veterinary use: specific questions on sterility to be addressed by ADVENT (EMA/CVMP/ADVENT/226871/2015)

A report on veterinary pharmacovigilance was recently published (EMA/CVMP/818155/2015). It describes the outcomes of post-marketing surveillance activities at the EMA level for veterinary medicinal products in 2015.

# Implementation of the ISO IDMP standards

The EMA will implement the standards for the identification of medicinal products (IDMP) developed by the International Organization for Standardization (ISO) to enable the identification of and exchange of high-quality and standardised data on medicines in the EU regulatory network. The EMA's SPOR project aims to prepare industry and regulators for compliance with the new standards and will deliver the systems managing the four domains of master data: Substances, Products, Organisations and Referentials.

The first two projects - Referentials Management Services (RMS) and Organisation Management Services (OMS) - are expected to be delivered in Q3 2016 (RMS) and Q4 2016 (OMS). They will provide the data foundation and technical services that will enable the implementation of Substance Management Services (SMS) and Product Management Services (PMS).

Stakeholders engagement plans, including SMEs, are being developed and will be shared in May 2016. For more information and the high level plan for SPOR, see Link.

# New therapies for rare diseases

A points to consider document for applicants to the Horizon 2020 call on new therapies for rare diseases has been published on the EMA website (EMA/819701/2015).

# Workshops, meetings and reports

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

**September 2015**

- Workshop on minimisation measures (Link)

**October 2015**

- Stakeholder meeting on product shortages due to manufacturing and quality problems (Link)

**November 2015**

- Workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants (DOACs) (Link)
- EMA/EUnetHTA meeting (Link)
- Expert meeting on paediatric development of fixed-dose combinations for the treatment of the human immunodeficiency virus (HIV) infection (Link)
- Workshop on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (Link)

**December 2015**

- European network of Paediatric research-EMA meeting on rare gastrointestinal and liver diseases (Link)

**January 2016**

- First annual bilateral meeting between EMA and the European Generic and Biosimilar Medicines Association (Link)

**February 2016**

- Workshop for micro-, small- and medium-sized enterprises on statistical perspectives in regulatory clinical development programmes - 5 February 2016 (Link)
- European Union International Organisation for Standardization (ISO) identification of medicinal products (IDMP) task force meeting (Link)

**March 2016**

- Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins (Link)

## Selection of upcoming events

**June 2016**

- EudraVigilance information day – 21 June 2016 (Link)

**October 2016**

- Information day on medication errors – 20 October 2016 (Link)

**December 2016**

- Workshop on measuring the impact of pharmacovigilance activities – 5 & 6 December 2016 (Link)

# Enterprise Europe Network (EEN)

The Enterprise Europe Network brings together around 600 business support organisations from more than 60 countries. The EEN helps small and medium-sized enterprises (SMEs) to make the most of business opportunities in the EU and beyond. The network advertises in particular opportunities to find the right partners for research & development projects, provides international connections to find new market opportunities, advises on access to funding and finance for projects and supports innovation and international growth. Further information on their activities and links to the local contact points are available on the EEN website (Link).

# Registered SMEs

Currently, 1495 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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