



# SME Office

# NEWSLETTER

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

<a href="#">Advanced therapy medicinal products</a>	1
<a href="#">Scientific guidelines for human medicines</a>	1
<a href="#">Clinical trials (CTs)</a>	2
<a href="#">Pharmacovigilance</a>	2
<a href="#">EMA-FDA parallel Scientific Advice pilot program for hybrid/complex generic products</a>	2
<a href="#">Medicines repurposing pilot programme</a>	2
<a href="#">Tailored SA for biosimilar developments</a>	3
<a href="#">Regulatory guidance</a>	3
<a href="#">Veterinary medicines</a>	4
<a href="#">COVID-19</a>	6
<a href="#">Events of interest and other news</a>	6
<a href="#">Innovation Horizon scanning</a>	7
<a href="#">Registered SMEs</a>	7
<a href="#">Contact details</a>	7

## Advanced therapy medicinal products

EMA published new flowcharts and checklist guidance on the quality, nonclinical and clinical development of advanced therapy medicinal products (see [webpage](#)).

## Scientific guidelines for human medicines

### Quality guidelines

A reflection paper on statistical methodologies for the comparative assessment of quality attributes in drug development ([EMA/CHMP/138502/2017](#)) was published on 27 July 2021. It provides regulatory considerations on statistical aspects for the comparative assessment of quality attributes in pre- and post-manufacturing changes, biosimilar and generic development settings.

An updated questions and answers (Q&A) on nitrosamines for marketing authorisation holders (MAHs) was published on 14 October 2021 ([EMA/409815/2020 Rev.6](#)). The document was revised on topics such as confirmatory testing by MAHs and manufacturers, and approaches for new and ongoing marketing authorisation applications (MAAs).

A new ICH guideline Q13 on 'continuous manufacturing of drug substances and drug products' was released for consultation until

20 December 2021 ([EMA/CHMP/ICH/427817/2021](#)). It provides clarifications on continuous manufacturing concepts and describes scientific approaches and regulatory aspects of continuous manufacturing of drug substances and drug products.

A revised ICH M7 guideline on 'assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk' was released for public consultation until 8 December 2021 ([EMA/CHMP/ICH/272147/2021](#)). The document was revised on topics such as HIV duration and amended with new monographs.

EMA is conducting a survey until **31 January 2021** for understanding the current status of chemistry, manufacturing and controls innovation in the European Union (EU). It will help identify any new developments as well as the priorities and expertise requirements of the future Quality Innovation Group (QIG). Additional information and the questionnaire can be found [here](#).

### Preclinical and clinical guidance

Revised product-specific bioequivalence guidance were published for lapatinib ([Link](#)), palbociclib ([Link](#)), acenocoumarol ([Link](#)) and dasatinib ([Link](#)).

The clinical pharmacology and pharmacokinetics Q&A ([Link](#)) was updated on topics including product-specific bioequivalence (see above) and biowaivers for fixed-combination products.

A revised ICH guideline E8 (R1) on '*general considerations for clinical studies*' will come into force on 14 April 2022 ([EMA/CHMP/ICH/544570/1998](#)). It provides updated guidance on the design, conduct and reporting of clinical trials by adopting quality by design principles to achieving fit-for-purpose data quality.

EMA published a new guideline on registry-based studies on 26 October 2021 ([EMA/426390/2021](#)). It addresses methodological, regulatory and operational aspects of using registry-based studies to support regulatory decision-making, and provides details on how to plan a study, design a protocol, select a patient population, analyse and report the data. It also contains appendices on safety reporting and the suitability of registries for registry-based studies.

## Clinical trials

The European Commission (EC) has confirmed that the entry into force of the Clinical Trial Regulation (CTR) and the go-live date for the clinical trial information system (CTIS) will be on 31 January 2022 (see [press release](#) and [summary of key areas in preparation of CTIS operation](#) for further information).

EMA has set up an extensive online modular training programme to help clinical trial sponsors prepare for CTIS ([Link](#)). In addition, EMA has published a new handbook ([Link](#)), which covers priority topics identified with clinical trial sponsors, with references and links to supporting material. To keep updated on CTIS, see also CTIS Highlights newsletters ([Link](#)) and the latest SME webinar ([Link](#)).

A user guidance on the electronic submission of information on investigational medicinal products for human use in the Extended EudraVigilance medicinal product dictionary (XEVMPD) was published ([EMA/186412/2021](#)). It describes how information for each Extended EudraVigilance product report message (XEVPRM) data element for a medicinal product entity should be completed. Clinical trials sponsors should read it in conjunction with the corresponding Q&A ([EMA/157035/2021](#)). See dedicated [webpage](#) for additional information.

## Pharmacovigilance

The XEVMPD training webpage ([Link](#)) on how to submit and retrieve medicinal product data using XEVMPD, also known as the 'Article 57 database', was updated including new step-by-step guides ([Link](#)) and an amended user manual ([EMA/308954/2012](#)).

Updated guidance documents and controlled vocabularies for the XEVPRM schema have been published, including new legal basis and authorisation procedure values available in the 'Article 57 database'. See dedicated webpage ([Link](#)) and 'how to submit information' ([Link](#)).

A revised list of important medical event (IME) terms was published on 23 September 2021 ([MedDRA version 24.1](#)). The list aims to facilitate classification of suspected adverse reactions for pharmacovigilance activities in the EU.

A new webpage on Data Analysis and Real World Interrogation Network (DARWIN EU) was published ([Link](#)). DARWIN EU aims to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the EU.

## EMA-FDA parallel Scientific Advice (SA) pilot program for hybrid/complex generic products

On 15 September 2021, EMA and Food and Drug Administration (FDA) launched a pilot program to provide parallel SA for complex generic products i.e. hybrid under Article 10(3) of Directive 2001/83/EC. The program aims to increase dialogue between agencies and applicants with a view to optimise product development, and minimise unnecessary testing. More information can be found in the general principles document ([Link](#)).

## Medicines repurposing pilot programme

EMA and the Heads of Medicines Agencies are launching a pilot project to support repurposing of medicines. The aim of this initiative is to support not-for-profit organisations and academia to generate evidence on the use of an established medicine in a new indication (see [press release](#) and [Q&A document](#)). As part of the pilot programme, EMA and national medicines agencies will provide tailored SA to help developers generate evidence to support a future application (see SA [webpage](#) for more information).

## Tailored SA for biosimilar developments

EMA published a report on experience with the tailored SA pilot programme (2017-2020) for biosimilar developments ([Link](#)). Additional information can be found in a Q&A document published on 17 October 2021 ([EMA/289230/2021](#)).



## Regulatory guidance

As of 1 November 2021, registration of new sites and organisations for centrally-authorized medicinal products in Organisation Management Service (OMS) will become mandatory prior to the associated regulatory submissions to the Agency (e.g. transfer of the marketing authorisation, addition of a manufacturing site). A Q&A document on the mandatory use of OMS in centralised procedure to support applicants and MAHs was published on 8 October 2021 ([Link](#)).

The following documents have been updated:

- Guidance on paediatric submissions via eSubmission Gateway and eSubmission Web Client on e.g. Research Product Identifier ([EMA/672643/2017 Rev. 4](#)).
- Paediatric investigation plans (PIP) Q&A ([Link](#)) on e.g. applying for a PIP, waiver or deferral, compliance statement, modifying an agreed PIP and requesting for class waivers confirmation.
- Explanatory notes on general fees payable to the EMA on e.g. parallel distributor, inspections invoicing ([Link](#)).
- Pre-authorization guidance ([EMA/821278/2015](#)) on topics including eligibility request, appointments of (co-) rapporteurs, MAAs submission timing, notification of change in contact person/intended submission date, accelerated assessment eligibility, pre-submission meeting, withdrawal of request, quality aspects regarding transfer of test methods for biological medicinal products and risk management plan.
- Post-authorization guidance ([EMA-H-19984/03 Rev. 94](#)) on topics including type II variations, post-authorization measures, transfers of MAs, marketing status updates and sunset clause monitoring.
- Q&A document, features list and project summary presentation on the European Medicines Regulatory

Network's Digital Application Dataset Integration (DADI) project to replace electronic application forms with new web-forms ([Link](#)).

- Checklists for initial notifications ([EMA/267299/2020 Rev. 2](#)) and annual updates for parallel distribution ([EMA/405782/2020 Rev. 2](#)) guidance for industry.
- General principles: EMA-FDA parallel SA ([Link](#)) on FDA contact point.
- IRIS guide – How to create and submit scientific applications, for industry and individual applicants ([EMA/444925/2018](#)).
- Procedural advice for orphan medicinal product designation – Guidance for sponsors ([EMA/420706/2018 Rev 11](#)) updated on how to describe the mechanism of action.
- Administrative validation checklist for initial MAAs by applicants ([Link](#)).
- Guide to information published on human medicines ([Link](#)).
- Compilation of Union procedures on inspections and exchange of information on topics including medicinal products quality defects management, good manufacturing practice (GMP) status verification in third countries manufacturers, update of GMP certificates ([EMA/INS/428126/2021 Rev 18](#)).

EMA has streamlined the pre-submission (PSM) interaction process with applicants by easing the administrative documentation burden and speeding up advice to applicants. EMA has updated its [pre-submission guidance](#) to reflect these changes, which also includes details on where a tailored meeting will be required for SMEs.

### Product information (PI)

EMA published a Q&A clarifying the consequences of Irish language derogation ending on 1 January 2022 ([EMA/699123/2021](#)). MAHs established in Ireland should request a language waiver where English is to be the authentic language selected for the PI and EC decisions (see dedicated [webpage](#)).

### Medical devices

A new guideline on quality documentation for medicinal products used with a medical device will come into effect on 1 January 2022 ([EMA/CHMP/QWP/BWP/259165/2019](#)). The document focuses on product-specific quality aspects of a medical device that may impact on quality, safety and efficacy of a medicinal product. It should be read in conjunction with the Q&A on the implementation of the medical device regulations ([Link](#)).

EMA is launching dedicated regulatory support to developers to replace, reduce and refine animal use for the development, manufacturing and testing of human and veterinary medicines. The action will be provided by EMA's Innovation Task Force (ITF) and facilitate the development and implementation of new approach methodologies in line with the 3Rs principles and EU legislation on the protection of animals used for scientific purposes. See innovation in medicines [webpage](#) and [press release](#) for additional information.



## Veterinary medicines

### Scientific guidelines

The ad-hoc ADVENT expert group will be replaced by the Novel Therapies and Technologies Working Party (NTWP). More information on the NTWP's responsibilities, composition, procedures and activities is available in the dedicated webpage ([Link](#)).

New scientific guidelines were released and will come into effect on 28 January 2022 on:

- Data requirements for adjuvants in vaccines for veterinary use ([EMA/CVMP/IWP/315887/2017](#)). It sets out the information to be included in parts 2, 3 and 4 of MAAs and in the summary of product characteristics (SPC).
- Manufacture of the veterinary finished dosage form ([EMA/CVMP/QWP/798401/2015](#)). It provides clarifications on information to include in MAAs with respect to manufacturing process description; it replaces guidance on the manufacture of the finished dosage form (EMA/CVMP/126/95).

EMA published a new [webpage](#) on limited markets under the new veterinary medicinal products regulation (VMR) (see Minor use/minor species and limited markets [webpage](#) for details on current policy application deadlines):

- Classification of a product for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (Applications for limited markets) ([EMA/CVMP/235292/2020](#)).

- Safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets under Article 23 ([EMA/CVMP/345237/2020](#)).
- Efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets under Article 23 ([EMA/CVMP/52665/2020](#)).
- Data requirements for applications for immunological veterinary medicinal products intended for limited markets under Article 23 ([EMA/CVMP/59531/2020](#)).

The following scientific guidelines were updated to align them with new definitions and terminologies provided by the VMR. The documents will come into effect on 28 January 2022:

- Conduct of efficacy studies for non-steroidal anti-inflammatory drugs (NSAIDs) ([EMA/CVMP/EWP/1061/2001-Rev.1](#)).
- Conduct of bioequivalence studies for veterinary medicinal products ([EMA/CVMP/016/2000-Rev.4](#)).
- Statistical principles for clinical trials for veterinary medicinal products ([EMA/CVMP/EWP/81976/2010-Rev.1](#)).
- Demonstration of palatability of veterinary medicinal products ([EMA/CVMP/EWP/206024/2011-Rev.1](#)).
- Demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish ([EMA/CVMP/EWP/459868/2008-Rev.1](#)).
- Dossier requirements for anticancer medicinal products for dogs and cats ([EMA/CVMP/28510/2008-Rev.1](#)).
- Efficacy requirements for ectoparasiticides in cattle ([EMA/CVMP/625/03-Rev.1](#)) and in sheep ([EMA/CVMP/411/01-Rev.1](#)).
- Veterinary medicinal products controlling *Varroa destructor* parasitosis in bees ([EMA/CVMP/EWP/459883/2008-Rev.1](#)).
- Testing and evaluation of efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats ([EMA/CVMP/EWP/005/2000-Rev.4](#)).
- Reflection paper on promoting authorisation of alternatives to antimicrobial veterinary medicinal products in the EU ([EMA/CVMP/143258/2021](#)).

MAHs will no longer need to submit periodic safety update reports from 28 January 2022 as continuous signal management will become mandatory. A guideline on veterinary good pharmacovigilance practices (VGVP guideline) will supersede current guidelines on veterinary pharmacovigilance. The six modules are available on a dedicated webpage ([Link](#)).

For information and updates on the VMR consult the Veterinary Medicines Regulation highlights newsletters ([Link](#)).

The following draft guidance documents were released for public consultation:

- Concept paper on a guideline development for MRL evaluation of biological substances for use in food-producing species ([EMA/CVMP/SWP/207500/2021](#)).
- Guideline on data requirements for authorisation of immunological veterinary medicinal products under exceptional circumstances under Article 25 of the VMR. ([EMA/CVMP/IWP/299554/2021](#)); it replaces guidelines on authorisations under exceptional circumstances for vaccines for emergency use against bluetongue (EMA/CVMP/IWP/37267/2008) and for vaccines for use in birds against avian influenza (EMA/CVMP/IWP/222624/2006).
- Guideline on data requirements for vaccine platform technology master files (vPTMF) ([EMA/CVMP/IWP/286631](#)); it elaborates on requirements and waivers for subsequent submissions after a first master file evaluation.
- Guideline on clinical trials with immunological veterinary medicinal products ([EMA/CVMP/IWP/260956/2021](#)); it provides guidance on criteria, data requirements and analysis for clinical efficacy and safety trials.
- Revised guideline on SPCs for antiparasitic veterinary medicinal products as defined in the VMR ([EMA/CVMP/EWP/170208/2005-Rev.1](#)); it replaces SPCs guideline on anthelmintics (EMA/CVMP/EWP/170208/2005).
- Guideline on determination of withdrawal periods for milk ([EMA/CVMP/SWP/735418/2012 Rev.1](#)).
- Guideline on determination of withdrawal periods for edible tissues ([EMA/CVMP/SWP/735325/2012 Rev.2](#)).
- Guideline on injection site residue ([EMA/CVMP/SWP/185470/2004 Rev.1](#)); it addresses the assessment of potential consumer risk from veterinary drug residues remaining at intramuscular and subcutaneous injection sites and the setting of pre-slaughter withdrawal periods.
- Reflection paper on interpretation of Article 72 of the VMR - Environmental safety documentation and environmental risk assessment (ERA) of certain veterinary medicinal products ([EMA/CVMP/ERA/245311/2021](#)); it proposes approaches for the identification of reference veterinary medicinal products (RVMPs) potentially harmful to the environment in line with the VMR, advises on ERA for RVMPs authorised before October 2005 and identified as potentially harmful to the environment, and harmonises information within the SPC harmonisation procedure.
- Concept paper on a guideline development on ERA of veterinary medicinal products intended to be used in aquaculture ([EMA/CVMP/ERA/173026/2021](#)).
- Concept paper on scientific guidelines for limited market products deemed not eligible for authorisation under Article 23 of the VMR ([EMA/CVMP/435071/2021](#)); recommends the development of a series of guidelines on data requirements flexibility for products only meeting the criterion of being intended for a limited market.

- Concept paper on an update of the reflection paper on the use of macrolides, lincosamides and streptogramins in food-producing animals in the EU: development of resistance and impact on human and animal health ([EMA/CVMP/AWP/266787/2021](#)).

### Veterinary product information (PI) templates

Revised PI templates supporting VMR requirements that will apply for initial MAAs validated on or after 28 January 2022 have been released in all EU languages (see veterinary PI dedicated [webpage](#) for additional information).

### Regulatory guidance

EMA has published new pre-authorisation procedural guidance ([Link](#)) applicable under the VMR to help companies prepare for MAA submissions after 28 January 2022.

Veterinary post-authorisation Q&A ([Link](#)) was updated with procedural guidance applicable under the VMR on topics including 'Sunset clause'.

The veterinary variations webpage ([Link](#)) (including currently applicable guidance) was updated to add guidance and procedural advice under the VMR ([Link](#)).

New or updated guidance have been published:

- Veterinary pre-authorisation guidance (currently applicable) on topics including pre-submission meetings ([Link](#)).
- Scientific and technical recommendations for implementing measures under the VMR on good pharmacovigilance practices ([EMA/CVMP/111028/2020](#)), pharmacovigilance system master files ([EMA/CVMP/123178/2019](#)), good distribution practices (GDP) ([EMA/567192/2019](#)), GDP for active substances used as starting materials ([EMA/87754/2020](#)) and scientific problem analysis and recommendations of oral veterinary medicinal products administered via routes other than medicated feed ([EMA/CVMP/508559/2019](#)).
- Various implementation guide chapters and guidance documents on veterinary medicines product data in the union product database (UPD) ([Link](#)).

### EMA fees

Revised explanatory notes on general fees payable to EMA were published on 25 October 2021 ([Link](#)) to reflect the entry into force of the VMR.

## Pharmacovigilance

A list of veterinary dictionary for drug regulatory activities (VeDDRA) low level terms and codes for reporting suspected adverse reactions in animals and humans to veterinary medicinal products that have become 'non-current' was published on 22 July 2021 ([Link](#)). It should be read in conjunction with guidance on the use of VeDDRA terminology ([EMA/CVMP/PhVWP/288284/2007-Rev.13](#)).

A revised combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products was published on 28 September 2021 ([Link](#)). It should be read in conjunction with the list of changes to combined VeDDRA list of clinical terms ([Link](#)) and the VeDDRA dataload friendly file including deprecated terms ([Link](#)). See EudraVigilance Veterinary [webpage](#) for additional information.

## COVID-19

EMA published new and updated guidance documents on :

- Variation applications for updates of vaccine composition for centrally authorised vaccines against COVID-19 disease ([EMA/175959/2021](#)).
- EMA initiatives for accelerating development support and evaluation procedures for COVID-19 treatments and vaccines ([EMA/213341/2020 Rev.3](#)).
- Updated Q&A documents on regulatory expectations for medicinal products for human ([Link](#)) and veterinary ([Link](#)) use during the COVID-19 pandemic on GMP and GDP topics (see also [GMP](#) and [GDP](#) webpages for additional information).

Latest updates, guidance for companies (e.g. on research and development, assessment, marketing authorisation, pharmacovigilance), information on treatments and vaccines, medicines availability, and public-health advice are regularly updated on EMA's dedicated webpage ([Link](#)).



## Events of interest and other news

Presentations, reports and/or videos of the following events have been published:

- Technical workshop on real-world metadata for regulatory purposes – 12/04/2021 ([Link](#)).
- Data standardisation strategy stakeholder workshop – 18/05/2021 ([Link](#)).
- Sixth industry stakeholder platform on research and development support – 04/06/2021 ([Link](#)).
- European network of paediatric research at EMA (Enpr-EMA) Coordinating Group and networks meeting – 29/06/2021 ([Link](#)).
- Sixth meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines – 30/06/2021 ([Link](#)).
- CTIS webinar: how sponsor organisations can prepare for CTIS – 29/07/2021 ([Link](#)).
- Nitrosamine implementation oversight group meeting – 09/09/2021 ([Link](#)).
- EMA IRIS Inspections Industry training on GMP & GCP – 10/09/2021 ([Link](#)).
- Union product database: webinar for marketing authorisation holders – 15/09/2021 ([Link](#)).
- Integration of EudraGMDP and OMS - Webinar for industry – 12/10/2021 ([Link](#)).
- Info day for SMEs: EMA support for SMEs under the new Veterinary Medicinal Products Regulation—28/10/2021 ([Link](#)).

### Other news

The following documents have been published:

- International Coalition of Medicines Regulatory Authorities (ICMRA) recommendations on common technical denominators for medicines traceability systems for interoperability ([Link](#)).
- ICMRA statement on pre-requisites for regulatory flexibility in pharmaceutical manufacturing change management ([Link](#)).
- 2016-2020 Transatlantic taskforce on antimicrobial resistance (TATFAR) [report](#) and [press release](#).

## Innovation Horizon scanning

**I**nternational Coalition of Medicines Regulatory Authorities (ICMRA) Informal Innovation Network - Horizon Scanning Assessment Report - Artificial Intelligence ([Link](#)).

EU-IN Genome editing Horizon Scanning Report ([Link](#)).

## Registered SMEs

**C**urrently, 1769 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 \(veterinary medicines\)](#)

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