

News from the EMA

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Assessment of human dietary exposure to residues of veterinary medicines in the EU

January 19, 2023

EMA and the European Food Safety Authority (EFSA) have published a joint report on the development of a harmonised approach to the assessment of dietary exposure of people to residues of veterinary medicines, feed additives, and pesticides in food of animal origin in the European Union (EU).

Veterinary medicines may leave residues in food derived from animal farming. Food can also contain residues of feed additives and pesticides to which animals have been exposed. In the EU, the presence of these residues is regulated to ensure the safety of consumers with legally binding maximum residue limits (MRLs) established. The establishment of MRLs relies on evaluations carried out by EFSA

and EMA, which include an assessment of human dietary exposure performed by modelling the level of residues to which people may be exposed.

However, different approaches are used in the assessments depending on whether the residues originate from veterinary medicines, feed additives or pesticides. While the methodologies are based on common principles, differences in the scientific approaches and practices can result in different outcomes.

To advance harmonisation, the European Commission (EC) mandated EFSA and EMA in 2020 to develop a common approach to the assessments. The Agencies set up a joint working group, composed of specialists with relevant

expertise. The working group developed a set of recommendations for each element of the exposure assessment, which were finalised after a public consultation that took place between June and September 2022. After that, the final report was adopted by EMA's Committee for Veterinary Medicinal Products (CVMP), endorsed by EFSA's Scientific Committee, and forwarded to the EC in December 2022.

The final report represents an important step towards harmonisation. If the recommendations are supported by the EC, their implementation in the different sectors will require a number of follow-up actions over the coming years. For veterinary medicines in particular, implementation of the recommendations will represent a very significant change to the way dietary exposure is assessed.

Mandatory use of CTIS from January 31, 2023, for all new clinical trial applications

January 31, 2023

On January 31, 2023, all initial clinical trial applications in the EU must be submitted via the Clinical Trials Information System (CTIS). CTIS is now the single-entry point for sponsors and regulators of clinical trials for the submission and assessment of clinical trial data. This follows a one-year transition, during which sponsors could choose whether to apply for a new clinical trial in the EU/EEA in line with the Clinical Trials Directive or under the new Clinical Trials Regulation (CTR), which entered into application on January 31, 2022.

In the past, sponsors had to submit clinical trial applications separately to national competent authorities (NCAs) and ethics committees in

each country to gain regulatory approval to run a clinical trial. Registration and the posting of results were also separate processes. With CTIS, sponsors can now apply for authorisations in up to 30 EU/EEA countries at the same time and with the same documentation. The system includes a public, searchable database for health-care professionals, patients, and other interested parties.

The CTR foresees a three-year transition period, from 2022 to 2025. The first milestone has been reached today; in the next two years, by January 31, 2025, all ongoing trials that were approved under the Clinical Trials Directive will be governed by the new Regulation and will have

to be transitioned to CTIS.

The application of the CTR strengthens Europe as an attractive location for clinical research. The new regulation streamlines the processes for the application and supervision of clinical trials, and their public registration: all clinical trial sponsors will now use the same system and follow the same procedures to apply for the authorisation of a clinical trial, no matter where they are located and which National Competent Authority (NCA) or national ethics committee they are dealing with.

The authorisation and oversight of clinical trials is the responsibility of EU/EEA Member States while the European Medicines Agency (EMA) is responsible for maintaining CTIS. The EC oversees the implementation of the Clinical Trials Regulation.



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A new role for EMA in monitoring and mitigating critical medical device shortages during public health emergencies

February 06, 2023

As of February 2, 2023, EMA's additional responsibilities regarding the monitoring and mitigation of shortages of critical medical devices during public health emergencies will apply. The new provisions are the last remaining part to be implemented of Regulation (EU) 2022/123, that reinforces EMA's role in crisis management of critical medicinal products and medical devices during public health emergencies.

The Agency is now responsible for coordinating responses of EU/EEA countries to shortages of critical medicines and medical devices including in-vitro diagnostics during public health emergencies. The Medical Devices Shortages Steering Group (MDSSG) will be set up to coordinate urgent actions within the Union in relation to the management of supply and demand issues of critical medical devices and to make recommendations to relevant stakeholders, including the EC, Member States, and notified bodies.

Once established, the MDSSG will be responsible for adopting lists of medical devices

which it considers to be critical for declared public health emergencies. These lists come with new reporting obligations for manufacturers of medical devices, authorised representatives and, if required, also for importers, distributors and notified bodies of those critical medical devices. Together with information from Member States this will enable accurate monitoring of the supply of and demand for these devices so that measures to prevent or mitigate potential and actual shortages can be taken swiftly and in a coordinated manner.

EMA will ensure that the MDSSG closely cooperates with the existing Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG) established in March 2022 during public health emergencies.

The MDSSG will be supported by the Medical Device Shortages SPOC Working Party (MD-SPOC WP) comprised of Single Points of Contact (SPOCs) for shortages from National Competent Authorities for medical devices, as well as by a sub-network of SPOCs from manufacturers of medical devices, authorised

representatives, importers, distributors, so-called Economic Operators (EO), and notified bodies.

The manufacturers, authorised representatives, importers, distributors of those critical medical devices included in any list of critical medical devices will need to register their single point of contact (EO-SPOC) through EMA's IRIS platform to facilitate rapid communication during a declared public health emergency. Relevant information, including supply and demand data, will be monitored via a reporting system.

Medical devices in the EU are regulated at national level, but EMA provides scientific opinions for certain categories of medical devices. The MDSSG will be composed of a representative of the Agency, a representative of the EC and one representative appointed by each Member State. The MDSSG will be co-chaired by the Agency and by a representative of a Member State. A representative of the Agency's Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP) may attend meetings of the MDSSG as observer.

Actions to support the development of medicines for children

February 06, 2023

Regulators in the EU have taken several initiatives in the past four years to increase the efficiency of paediatric regulatory processes and boost the development of medicines for children. These achievements are highlighted in the closing report of the EMA and EC action plan on paediatrics.

Some of the key improvements brought by the paediatric action plan include:

- **Strengthened focus on unmet medical needs:** Over the last four years, EMA and relevant stakeholders systematically got together to better identify and raise awareness on the areas where medicines for children are particularly needed, with a goal to shift the research agenda to these areas. For example, multi-stakeholder strategy fora to discuss and agree the needs of children with cancer, and of children with inflammatory bowel disease have taken place. The learnings from these meetings involving clinicians, paediatric patients and their representatives, academia, regulators, HTAs bodies, and developers are being taken into account by EMA when discussing paediatric investigation plans (PIPs) for new medicines.
- **Adapting regulatory processes to better support innovation:** To facilitate the establishment of PIPs, regulatory processes have been adapted and processes overall simplified. A major outcome of this work is the launch of a pilot phase for a “stepwise PIP” agreement:

under this framework, it will be possible in certain cases to agree on a partial development programme, conditional on the development of a full PIP once evidence becomes available over time. This will allow agreeing on PIPs for innovative medicines where crucial information needed to define certain parts of the plan is not yet available, while planning the conditions and milestones for companies to return to EMA’s paediatric committee (PDCO) and discuss the uncertainties once more data are available. More information on this newly developed framework, launched today, is provided in the guidance for a stepwise PIP pilot.

- **Increased alignment of data requirements between decision-makers:** To facilitate the compatibility of paediatric requirements between regulators, EMA has strengthened its collaboration with international partners, and notably within its paediatric cluster with the US Food and Drug Administration (FDA) and other international regulators. Work was also carried out through the European network of paediatric research at EMA (Enpr-EMA) to align international requirements for paediatric clinical trials authorisation and standards.

In 2017, the EC published a 10-year report on the implementation of the Paediatric Regulation. This report showed an overall success of the Regulation with an increase in authorised

medicines for children, but also identified some challenges, noting in particular that certain therapeutic areas (e.g., oncology, neonatology) still lacked sufficient developments for children.

On the basis of this report, EMA together with the EC held a multi-stakeholder workshop in 2018 to identify ways to improve the implementation of the Paediatric Regulation. As a result of this workshop, the paediatric action plan was developed to provide some immediate solutions to these challenges under the current regulatory framework. This work will contribute to the application of the Paediatric Regulation, while the EC is currently finalising a proposal to revise the EU’s pharmaceutical legislation, which will include a revision of the legislative framework applicable for medicines for children. The adoption of the proposal is expected next month.

The Paediatric Regulation came into force in the EU in 2007 to encourage manufacturers to research and develop medicines for children’s specific therapeutic needs by using a system of rewards and obliging developers to specifically plan the development of their medicine for children (e.g., by integrating it into the development for adults) and submit a corresponding PIP. A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for paediatric patients. All applications for marketing authorisation for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver.



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New features further strengthen Priority Medicines scheme (PRIME)

April 04, 2023

EMA is introducing a number of new features to the PRIME scheme to strengthen its support for the development of medicines in areas of unmet medical needs. The PRIME scheme enables earlier availability of life-changing medicines for patients. By the end of 2022, 26 medicines that benefited from PRIME support had received a positive recommendation for approval in the EU.

EMA published a report presenting results from the first five years of PRIME in March 2022. It looked at how the scheme helped developers prepare for marketing authorisation assessments. This report showed that the PRIME scheme has had a positive impact on the authorisation of new medicines that benefit patients with no current treatment options for their disease or offer a major therapeutic advantage over existing treatments. It also called for further enhancement, including increasing the flexibility of scientific

advice provision, and helping applicants better prepare for the marketing authorisation assessment phase. The implementation of the new features follows from this review.

To optimise the early scientific and regulatory support provided to promising medicines, a roadmap for each PRIME development alongside a product development tracker will be established. Both tools will facilitate the continuous dialogue between regulators and developers as the progress of the development is continuously monitored and as critical aspects for further discussion can be identified throughout the development process.

Starting as a 12-month pilot until March 2024, expedited scientific advice can now be provided specifically for PRIME developments in case of issues with a specific development programme that has already received comprehensive initial advice. This agile setting for

scientific advice will allow to address queries from PRIME applicants in a shorter timeframe.

The final new feature is represented by submission readiness meetings, which will be held approximately one year ahead of the submission of a marketing authorisation application with developers of PRIME medicines. The scope of these meetings is to discuss the status of the development including the implementation of previous regulatory advice, and the resulting data package intended to support the marketing authorisation application. Prospective applicants would also be expected to present mature plans for post-marketing evidence generation, as applicable.

All these initiatives aim to facilitate and accelerate the generation of robust and relevant evidence for the evaluation of a marketing authorisation application, which will give patients earlier access to transformative treatments that can make a real difference.

Single-arm trials as pivotal evidence for the authorisation of medicines in the EU

April 04, 2023



Photo: Freepik

EMA has opened a public consultation on a reflection paper¹ that discusses key concepts for single-arm clinical trials that are submitted as pivotal evidence in support of marketing authorisation applications for medicines in the European Union (EU). This is the first guidance document by an international medicine regulator articulating the considerations and challenges associated with this type of clinical trials. Stakeholders are invited to send their comments via an online form by midnight (CET) on September 30, 2023.

Randomised clinical trials (RCTs) in which a new treatment is compared against a placebo or an existing standard of care are widely considered as the gold standard for generating evidence needed by regulatory authorities to assess the efficacy and safety of a new medicine. In RCTs, patients are randomly assigned to either the active treatment or the control arm. Usually, large numbers of patients are included for these trials to generate robust data on the efficacy of a treatment.

In certain areas such as rare diseases,

including rare cancers, where target populations of new medicines are often very small, a proportion of marketing authorisation applications are submitted to EMA with clinical data from single-arm trials as pivotal evidence. Because there is no randomised comparator in a single-arm trial, all patients in the trial receive the experimental treatment and only the outcomes under the experimental treatment can be observed.

The reflection paper outlines considerations on single-arm trials that are submitted as pivotal evidence to demonstrate efficacy in a marketing authorisation application. It aims to stimulate the scientific discussion around key concepts and challenges associated with single-arm trials and to improve their design and conduct.

The reflection paper has been adopted by EMA's human medicines committee (CHMP) with contributions from the Committee for Advanced Therapies (CAT), the Methodology Working Party (MWP) and the Oncology Working Party (ONCWP).

Following the public consultation, comments from stakeholders will be analysed and considered in the final document that is planned to be published in 2024.

Reference

1. EMA/CHMP/564424/2021. Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation. April 21, 2023.

Reducing risks to human and animal health from exposure to N-methyl pyrrolidone in veterinary medicines

April 14, 2023

On December 8, 2022, EMA's veterinary medicines committee, the CVMP, recommended new measures to reduce the risks from exposure to the excipient N-methyl pyrrolidone (NMP) for women who may handle NMP-containing veterinary medicines and animals that are given these medicines. The recommendations address inconsistencies in the product information of veterinary medicines containing NMP, which are marketed in many EU Member States.

NMP is an excipient used in some veterinary medicines that is classified as a

teratogen (a substance that can cause birth defects following exposure during pregnancy) in laboratory animals. There is therefore the possibility that NMP could cause birth defects in children of women who handle or come into contact with NMP-containing medicines during their pregnancy, and in the offspring of animals given these medicines.

More than 1,100 veterinary medicines containing the excipient NMP are available in the EU under various trade names and in different formulations, for use mainly in companion animals and large farm animals.

These medicines are available as injections, solutions for infusion, spot-on and pour-on products, shampoos, sheep dips, sprays and concentrates for oral solutions for use in the drinking water of animals, or solutions for fish treatment.

The review of veterinary medicines containing NMP is the first referral under Article 82 of Regulation (EU) 2019/6 which was introduced as part of the new EU veterinary medicinal products regulation. The CVMP recommendations were sent to the EC, which issued an EU-wide legally binding decision on March 28, 2023.