

News from the EMA

More information can be found on the Agency's website: www.ema.europa.eu.

The articles included in this section are a selection from the European Medicines Agency's news and press release archive for November 2015 to March 2016.

European Medicines Agency guidance on methods to be used in the design and conduct of post-authorisation efficacy studies

November 6, 2015 – The European Medicines Agency (EMA) has released a draft scientific guideline that outlines how post-authorisation efficacy studies (PAES) should be designed by companies to support regulatory decision making in the European Union (EU). In addition, a guidance that describes the regulatory aspects for the fulfilment of imposed PAES is also published.

These studies are conducted within the authorised indication after a medicine has been granted a marketing authorisation, to collect data on aspects of its benefits that can only be or need to be explored once the medicine is marketed. In particular, PAES can address questions related to the benefits of a medicine stemming from the way it is used in everyday medical practice, including in specific populations, in relation to its use with other medicines or over time, and when there are changes in the understanding of a disease or the medicine's mechanism of action. The knowledge generated by these studies complements the information about the medicine's benefits that was assessed during its approval process.

These studies can be imposed by regulators

or may be carried out voluntarily by companies. The situations where a PAES can be required by medicines regulatory authorities in the EU were specified by the European Commission in April 2014. Prior to that date, regulators could request these types of studies in certain cases such as in the context of conditional marketing authorisations, authorisations under exceptional circumstances, paediatric use or referral procedures.

PAES can now be required for medicines with a standard marketing authorisation:

- At the time a marketing authorisation is granted, if new data indicate that the benefits of the medicine should be further studied.

The results of these studies should translate into better labelling and better use of medicines by patients and prescribers in clinical practice.

The draft scientific guideline applies to imposed and voluntary PAES. It has been developed in collaboration with the EU Member States and other interested parties and was released for a three-month public consultation. At the time of writing this article, additional regulatory and procedural guidance was planned for release together with the scientific guidance to clarify aspects in relation to the imposition of PAES, including the submission of study protocols by companies and their assessment by

SECTION EDITORS



Section Editor:

Anuradha Alahari

Anuradha.Alahari@parexel.com



EMA contact:

Monika Benstetter

press@ema.europa.eu

EMA, the assessment of the study results, and the possible regulatory outcomes following the conduct of an imposed PAES.



Launch of PRIME – Paving the way for promising medicines for patients

March 7, 2016 – The EMA launched its new PRIME (PRiority MEDicines) scheme to strengthen support to medicines that target an unmet medical need. The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the EU.

Through PRIME, EMA offers early, proactive and enhanced support to medicine developers.

PRIME builds on the existing regulatory framework and available tools such as scientific advice and accelerated assessment. By engaging with medicine developers early, PRIME aims to strengthen clinical trial designs to facilitate the generation of high quality data for the evaluation of an application for marketing authorisation. Early dialogue and scientific advice also ensure that patients participate in trials that are likely to provide the necessary data for an application for marketing authorisation, and help to make best use of limited resources.

To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Once

a candidate medicine has been selected for PRIME, the Agency:

- Appoints a rapporteur from EMA's Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy, to provide continuous support and help to build knowledge ahead of a marketing authorisation application.
- Organises a kick-off meeting with the CHMP/CAT rapporteur and a multi-disciplinary group of experts from relevant EMA scientific committees and working parties, and provides guidance on the overall development plan and regulatory strategy.

Increasing access to reports on adverse reactions to medicines

December 18, 2015 – The EMA will give increased access to reports on suspected adverse reactions to medicines authorised in the EU, while guaranteeing that personal data will be fully protected. This is the outcome of a revision of EudraVigilance Access policy, which was adopted by EMA's Management Board at its December 2015 meeting. The adoption followed a broad public consultation generating close to 400 comments which have been taken into account in the final policy.

EudraVigilance is the European database of all suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA). Managed by EMA on behalf of the EU medicines regulatory network, EudraVigilance receives over one million adverse drug reaction (ADR) reports per year.



The large datasets included in the database provide the backbone for the continuous safety monitoring of medicines in the EU.

The Agency has made data from EudraVigilance publically available since 2011. At the time, EMA defined levels of access to information on ADR reports for medicines in EudraVigilance per stakeholder group: for European regulators, for healthcare professionals, consumers and patients, for marketing authorisation holders and for academia. Information from EudraVigilance on centrally authorised products and substances commonly used in medicines is available through a dedicated public website.

The revised policy takes into account the changes to the system of safety monitoring of medicines introduced by the pharmacovigilance legislation, such as new transparency provisions, the introduction of direct patient reporting across all EU Member States and a simplification of the reporting of adverse reaction reports for pharmaceutical companies.

Key changes include:

- The public will have access to more information, including line listings of the side effect reports and summary presentations for individual adverse reaction reports received in EudraVigilance. While ensuring that patients and those who have sent in reports of suspected side effects are not identifiable, this access represents a significant increase in transparency for the users of medicines.
- Academia will be able to get extended access to data sets upon request in support of their research activities.
- The Uppsala Monitoring Centre (UMC) of the World Health Organization (WHO) will

be added as a new stakeholder group who will be provided with individual case safety reports (ICSRs) originating from within the EEA.

- Medicines regulatory authorities in countries outside the EEA will be provided with data, in line with the WHO dataset, upon request.
- Marketing authorisation holders of medicines authorised in the EU will be given enhanced access to reports related to their medicines in support of their signal detection and other pharmacovigilance obligations.

These changes will come into effect in the third quarter of 2017 in parallel with EMA implementing a series of technical improvements to the EudraVigilance system.

Data transfer agreement with WHO

To allow the transfer of data on suspected adverse reactions occurring in the EEA, EMA and the WHO concluded an agreement earlier this month. The data will be transferred electronically to WHO's UMC on a daily basis. The start of this data transfer in 2017 will follow the introduction of the new reporting rules within the EEA which take effect after a successful audit of the improved EudraVigilance system.

The transferred reports on suspected adverse reactions occurring in the EEA will contribute to VigiBase, the WHO Global Individual Case Safety Report database, on behalf of the WHO Programme on International Drug Monitoring. Better global knowledge on the safety of medicines will also help to promote the safe use of medicines for the benefit of patients worldwide.

- Assigns a dedicated EMA contact point.
- Provides scientific advice at key development milestones, involving additional stakeholders such as health technology assessment bodies to facilitate patients' quicker access to the new medicine.
- Confirms potential for accelerated assessment at the time of an application for marketing authorisation.

While PRIME is open to all companies on the basis of preliminary clinical evidence, micro-, small- and medium-sized enterprises (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. They may

also request fee waivers for scientific advice. Since SMEs and academia often lack experience with the regulatory framework, they can benefit in particular from earlier scientific and regulatory advice.

Strengthened regulatory toolkit for medicines addressing unmet needs

EMA has released guidance documents on PRIME as well as a comprehensive overview of the EU early access regulatory tools (accelerated assessment, conditional marketing authorisation and compassionate use). Revised guidelines on the implementation of accelerated assessment and conditional marketing authorisation have also been published. All these tools are reserved for

medicines addressing major public health needs. Although PRIME is specifically designed to promote accelerated assessment, it will also help to make best use of other EU early access tools and initiatives, which can be combined whenever a medicine fulfils the respective criteria.

PRIME was developed in consultation with the Agency's scientific committees, the European Commission and its expert group on Safe and Timely Access to Medicines for Patients (STAMP) as well as the European medicines regulatory network. The main principles of PRIME were released for a two-month public consultation in 2015 and the comments received were taken into account in the final version.

Handling competing interests: revised rules for Management Board members

January 14, 2016 – The EMA has published its revised policy on handling competing interests for members of its Management Board. The revised policy was adopted at the December 2015 Board meeting. The revision aligns EMA's Management Board policy with the Agency's policy on handling declarations of interests for scientific committee members and experts which underwent a major overhaul.

In order to ensure that its scientific experts, staff and Management Board do not have any financial or other interests in the pharmaceutical industry that could affect their impartiality, EMA, over recent years, has continuously reviewed and fine-tuned its policies taking into account experience obtained. The Management Board takes strategic decisions and oversees [sic] corporate activities of the Agency, such as setting EMA's budget and approving its annual work programme. It does not give recommendations on marketing authorisations of medicines.

The Agency will apply a 'risk-based' approach, to determine the level of involvement in activities of the Management Board for a Board member with a declared interest. This approach is based on four factors:

- The nature of the declared interest
- The timeframe during which the interest occurred
- The type of Management Board activity and the likely impact of the Board's decision on the pharmaceutical, or other industry
- The type of action requested by the Management Board, e.g., whether a decision such as approval or endorsement has to be taken by the Board or not.

The new policy will enter into force on 1 May 2016.

Breach of trust procedure

The current "breach of trust" procedure on declarations of interests for Management Board members has also been revised and was approved by the Board in December 2015. Changes are aligned with those introduced in 2015 for the breach of trust procedure for the scientific committee members and experts. The breach of trust procedure was developed in 2012 to deal with cases of incorrect or incomplete declarations of interests of Board members. The revised breach of trust procedure came into effect on 1 January 2016.



EMA sets up task force on Zika virus

February 8, 2016 – The EMA has established a task force of European experts with specialised knowledge in vaccines, infectious diseases and other relevant expertise to contribute to the global response to the threat of the Zika virus infection. This group will be available to give advice on any scientific and regulatory matters for the research and development of medicines or vaccines against the virus.

The EMA task force was established following the declaration by the WHO on 1 February 2016 that the Zika virus outbreak is a Public Health Emergency of International Concern. There are currently no anti-Zika virus vaccines or medicines that are approved or undergoing clinical studies. The Agency is encouraging medicine developers to contact EMA if they have any promising projects in this area. EMA will also

proactively reach out to companies already planning to work on investigational vaccines and offer scientific and regulatory advice. EMA will review any new information as soon as it becomes available to support the response to this widening public health crisis.

During a health emergency such as the Zika virus outbreak, EMA works closely with European bodies, including the European Commission and the European Centre for Disease

Prevention and Control (ECDC) and with international partners such as WHO and other international regulators from affected countries.

Existing mechanisms available to support medicines' developers

There are already a number of existing mechanisms and tools which can be used to help speed up the research and development of medicines and vaccines in the context of an emerging viral disease such as Zika. Companies may seek scientific advice from EMA on the appropriate tests and studies required in the development of their products. Early and regular interaction with the Agency can significantly speed up the development of medicines. The European Article 58 procedure also provides an opportunity to give a scientific opinion on treatments intended primarily for use in non-EU countries, while collaborating closely with WHO and experts from those countries.



Consultation on revised guideline on medicines to treat Alzheimer's disease

February 1, 2016 – The EMA has released a revised guideline on medicines for the treatment of Alzheimer's disease and other types of dementias for a six-month public consultation. Stakeholders are invited to send their comments by 31 July 2016 to: cnswpsecretariat@ema.europa.eu using the template provided.

According to the WHO, 35.6 million people have dementia worldwide and this number is expected to double by 2030. Recent progress in understanding the pathophysiology of Alzheimer's disease suggests that the biological changes associated with the disease start to occur as early as 10 to 20 years prior to the emergence of clinical symptoms. Experimental medicines should therefore be evaluated in earlier disease stages as certain treatments may be more effective at that stage than later in the illness.

EMA considers dementia as a key public health priority and follows a multi-stakeholder approach to facilitate research and development of more effective medicines. The revised guideline takes into account comments received at EMA's workshop on the clinical investigation

of medicines for the treatment of Alzheimer's disease in November 2014. This workshop brought together a wide range of stakeholders, including patient representatives, regulators, pharmaceutical industry and independent experts. The aim of the workshop was to ensure that during the revision of its guideline, EMA would be able to consider the most up-to-date scientific developments in understanding and treating Alzheimer's disease and views from experts in the field. The revised guideline also builds on EMA scientific advice provided for a number of specific development plans for Alzheimer's disease in recent years, as well as the qualification of several biomarkers for the selection of patients in clinical trials.

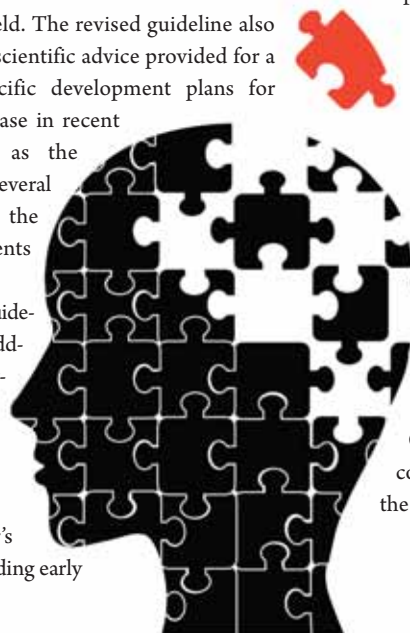
The revised guideline specifically addresses the following:

- The impact of new diagnostic criteria for Alzheimer's disease, including early

and even asymptomatic disease stages, on clinical trial design.

- The choice of parameters to measure trial outcomes and the need for distinct assessment tools for the different disease stages in Alzheimer's (different signs and symptoms, differences in changes over time, severity).
- The potential use of biomarkers and their temporal relationship with the different phases of Alzheimer's disease at different stages of medicine development (mechanism of action, use as diagnostic test, enrichment of study populations, stratification of subgroups, safety and efficacy markers, etc.).
- The design of long-term efficacy and safety studies.

Comments received during the consultation will be taken into account in the finalisation of the guideline.



Guidance for the publication of clinical data

March 3, 2016 – The EMA has published detailed guidance for pharmaceutical companies on the requirements to comply with its policy on the publication of clinical data. EMA's pioneering policy entered into force on 1 January 2015 and applies to clinical reports contained in all marketing authorisation applications submitted on or after this date. The first reports are currently foreseen to be publicly available in September 2016.

The guidance consists of four chapters:

- The first chapter is an overarching introduction with information on the scope and definitions used throughout the text.
- The second chapter details procedural aspects on the submission of clinical reports including the concrete processes.
- The third chapter gives guidance to companies on how to anonymise clinical reports for

the purpose of publication. EMA recognises that a number of methods are available to make sure the data is presented in a form that does not allow re-identifying individuals who have participated in clinical trials. Therefore the guidance does not single out one specific anonymisation method yet gives recommendations to companies on how to best balance data utility for researchers with a minimal risk of re-identification. Companies will need to provide a report explaining their approach to the anonymisation of the data, which will be reviewed and published by EMA.

- The fourth chapter focuses on the identification and redaction of commercially confidential information (CCI) in clinical reports submitted to EMA for the purpose of publication. The guidance makes clear that the vast majority of the information contained in clinical reports is not considered CCI. However, in the limited circumstances in

which clinical reports might contain CCI, companies will need to submit to EMA for review a table justifying why such data has been redacted. The guidance clarifies which type of data EMA would typically refuse as being CCI and how the redaction of such data will be handled.

This detailed set of guidance has been finalised following an extensive consultation with all stakeholders concerned throughout 2015.

To further ensure that companies are well prepared for the proactive publication of clinical data, EMA will now start reaching out to companies which are concerned by the first wave of publication, i.e. those for which the decision making process has been finalised since the policy entered into force. In addition, EMA will organise a webinar in the second quarter of 2016 to allow companies to ask any outstanding practical questions. This webinar will be live broadcast and will be available for future reference on the EMA website.