News from the EMA

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More information on the work of the EMA can be found on its website: http://www.ema.europa.eu.

European Medicines Agency agrees policy on publication of clinical trial data with more user-friendly amendments

12 June 2014 – The European Medicines Agency Management Board on 12 June 2014 agreed the policy on publication of clinical trial data, together with more user-friendly amendments proposed by EMA Executive Director Guido Rasi, that will not only allow the Agency to proactively publish clinical trial data that are submitted as a part of marketing authorisation applications, but also give the possibility to download, save, and print the trial data for academic and non-commercial research purposes.

In light of discussions at the Board, the wording of the policy, including practical arrangements for academic and non-commercial research users, will now be finalised with a view to its adoption by the Board through written procedure by mid-July 2014, and will be effective from 1 October 2014. Importantly, the Agency will ensure that the policy will not prejudice citizens' rights under existing access to documents legislation and the new clinical trials regulation.

Since embarking on its plans for the proactive publication of clinical trial data, the Agency has aimed to achieve the broadest possible consensus among its stakeholders and their often competing views and interests. After an extensive consultation phase that took place between June and September 2013, the Agency carried out a second round of targeted consultation in May 2014 that showed broad support for the policy, but highlighted concerns over the proposed view-on-screen-only access.

The Agency's policy is an important step forward towards achieving increased transparency in the regulation of medicines in Europe. It takes the Agency beyond its legal obligations and provides an unprecedented level of access to clinical trial data that are used as a part of decision making for new medicines.

Regulatory information – Companies now required to update, complete, and improve quality of information on authorised medicines submitted to the European Medicines Agency

16 June 2014 – From today, the European Medicines Agency requires marketing-authorisation holders to update the information on authorised medicines that they have submitted in accordance with Article 57(2) of the 2010 pharmacovigilance legislation.

This includes completing previously submitted information with additional data elements included in the new data-submission format, bringing medicine information up-to-date, and checking that the quality of the information is in line with the updated reporting requirements.

Companies need to complete this process by the end of 2014.

The additional elements that are now required include:

- the details of the legal basis of the marketing authorisation;
- a description of the medicinal product type based on controlled vocabularies;
- information on the authorised pharmaceutical form and before reconstitution into the 'administered' pharmaceutical form;
- a description of the size of the marketing-authorisation-holder company.

From today, the data submission system will only accept submissions that are in line with the updated data-submission format. From July 2014, the Agency is planning to begin a systematic review of the quality and integrity of the information submitted, to ensure that it is accurate and up-to-date.

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This information on medicines is being used to support pharmacovigilance data analysis, to facilitate medicines regulation and fulfil regulatory actions and legal obligations, and to strengthen communication with the Agency's stakeholders and partners. By streamlining the identification of products relevant to pharmacovigilance procedures, this database is expected to simplify adverse reaction reporting for marketing-authorisation holders and ensure that fees are calculated accurately.

Since January 2014, the Agency has been releasing guidance documents to support marketing-authorisation holders in these tasks. These include updates to the legal notice, detailed technical guidance, a data quality control methodology, and controlled vocabularies.

The Agency has also published two new guidance documents today concerning the splitting of the full presentation names and substance names best practice.

In addition to completing previously submitted information, marketing-authorisation holders need to continue to submit information on new marketing authorisations within 15 calendar days from the date of notification of the granting of the marketing authorisation by a regulatory authority. If companies using the EudraVigilance Gateway to submit data cannot provide this information within this timeframe because of the schema changes, they should inform the Agency of their expected submission plan by emailing art57submissionplan@ema.europa.eu and provide their name, headquarter ID, volume of data, and timeline for submission.

The Agency has been working closely with representatives of European pharmaceutical industry associations on the development of these measures through the Joint Implementation Working Group. The Group has endorsed all of the aspects related to the planning of and guidance on the data maintenance submission process.

In line with Article 57(2) of the 2010 pharmacovigilance legislation, all holders of marketing authorisations for medicines in the European Union (EU) must submit information to the European Medicines Agency on all medicines authorised for use in the EU and keep this information up-to-date. This includes:

- nationally authorised medicinal products (NAPs);
- centrally authorised medicinal products (CAPs);
- mutually recognised medicinal products (MRPs);
- decentrally authorised medicinal products (DCPs).

Marketing-authorisation holders are also required to submit to the Agency information on all medicines for which they hold a marketing authorisation in European Economic Area (EEA) countries outside the EU (i.e. Iceland, Liechtenstein, and Norway) since the pharmacovigilance legislation has been incorporated into the EEA agreement.

Marketing-authorisation holders were initially required to submit information on all human medicines authorised in the EU by 2 July 2012. Since July 2012, marketing-authorisation holders have also had to submit information on new marketing authorisations granted after 2 July 2012.

Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014

19 June 2014 – As of 21 July 2014, it will become mandatory for sponsors to post-clinical trial results in the European Clinical trials Database (EudraCT), managed by the European Medicines Agency (EMA). This date corresponds to the finalisation of the programming of the database as referred to in a European Commission guideline, in application of the current clinical trials Directive 2001/20/EC and the Paediatric Regulation. Under these frameworks, since the result-related information is fed into the publicly accessible European Union Clinical Trials Register, summary results of clinical trials will become available to the public as sponsors start to comply with their legal obligations.

What this means for clinical trial sponsors

Sponsors will now be obliged to post results in EudraCT for any interventional trials registered in EudraCT and that have ended within a certain period of time:

- For any interventional clinical trials that ended on or after 21 July 2014, sponsors will have to post results within 6 or 12 months following the end of the trial, depending on the type of trial concerned;
- For trials that ended before that date, sponsors will need to submit the results retrospectively, in accordance with the specific timeframe laid out in the above-mentioned European Commission guideline on the posting and

publication of result-related information on clinical trials.

EudraCT already contains protocol-related information submitted by sponsors for interventional clinical trials conducted in European Economic Area (EEA) countries, as well as clinical trials conducted in third countries, when the clinical trial is part of an agreed Paediatric Investigation Plan (PIP). Information on these is already made public in the European Union Clinical Trials Register.

Clinical trial sponsors were encouraged to start uploading summary results on a voluntary basis, when new functionalities were made available in EudraCT in October 2013. This was intended to enable them to get used to this new feature and be ready to comply with the legal requirements.

A further iteration of EudraCT was launched at the beginning of May 2014 with improved functionalities. The scope of the information to be posted in EudraCT has also been extended to include marketing-authorisation holder sponsored clinical trials conducted in third countries that involve the use in the paediatric population of a medicinal product covered by an EU marketing authorisation.

As of 21 July 2014, with the launch of a final iteration of EudraCT, all functionalities will be in place to enable the posting of results by sponsors on a compulsory and systematic basis.

What this means for public access to information on clinical trial results

A subset of the data included in EudraCT is made available to the public in the European Union Clinical Trials Register. The content and level of details of these summary results are set out in the European Commission guideline and in its technical guidance. A number of summary results can already be viewed on the European Union Clinical Trials Register website. A typical set of summary results provides information on the objectives of a given study, explains how it was designed, and gives its main results and conclusions.

In addition, information on paediatric studies that ended before the Paediatric Regulation came into force in 2007, which used to be accessible through the EMA website, is now available through the European Union Clinical Trials Register. This improvement allows a greater and richer approach to the search and greater public access to clinical trial-related information.

It is foreseen that access to summary results will be an essential feature of the European Union Clinical Trials Register for interventional clinical trials conducted in EEA countries, as well as clinical trials conducted in third countries which are linked to European paediatric drug development.

Outcome report on first European collaboration between regulators and HTA organisations: improving the contribution of regulatory assessment reports to health technology assessment

25 June 2014 – The report of an initiative undertaken jointly by the European Medicines Agency (EMA) and the European network for Health Technology Assessment (EUnetHTA) to make regulators' reports about scientific assessments of medicines better usable by health technology assessment (HTA) bodies has been published in *Value in Health*, the Journal of The International Society for Pharmacoeconomics and Outcomes Research.

The article, entitled 'Improving the contribution of regulatory assessment reports to health technology assessments – a collaboration between the European Medicines Agency and the European network for Health Technology Assessment',[1] is authored by staff members of the EMA and representatives of EUnetHTA. This work was the first joint project between regulators and HTA bodies on a European level and is part of their ongoing dialogue to support policy-maker decisions in the future.

Clinical data generated by pharmaceutical companies during the development process of a medicine is the basis for the evaluation of the benefit/risk balance of a medicine for the purpose of marketing authorisation. The same data informs the assessment of the effectiveness of the new medicines compared to existing therapies, as part of the HTA process to support decision making on appropriate utilisation, price, and reimbursement in EU Member States.

The joint EMA-EUnetHTA project responded to a political recommendation to consider how the assessment of the favourable and unfavourable effects of a medicine as contained in the EMA's European Public Assessment Reports (EPARs) can best be used to inform the assessment of the relative effectiveness of new medicines for HTA purposes in EU Member States. As part of this project, the EMA and EUnetHTA developed an improved structure and presentation of key information with the view to increase clarity and transparency of the outcome of the scientific-review process as reflected in the EPARs.

'With the improved presentation of data and information in the EPAR it is envisaged that this

regulatory document through harmonised efficacy data presentation will be more useful in the context of rapid relative effectiveness assessments by HTA bodies when they inform policy makers and healthcare decision makers in the future', explained the authors.

Beyond the EPARs project, the EMA and EUnetHTA are continuing to explore other areas of collaboration or exchange of information. These include ways for sponsors to obtain scientific advice or early dialogues with regulators and HTA or payer bodies, discussions and exchange on scientific and methodological guidelines, exploring opportunities of exchange on regulatory assessments in view of subsequent HTAs, post-licensing data generation and the specificities of orphan medicinal products. Regular meetings are held between EMA and EUnetHTA, most recently on 15 May 2014. Minutes from these meetings are made available on the websites of both the EMA and EUnetHTA, as is the joint 3-year work plan.

The value of cooperation between regulators and HTA bodies has a real potential to reduce the time for a medicinal product to reach patients. It also has potential to reduce development costs for sponsors by shaping medicines development programmes so that they generate data relevant for the needs of both regulatory authorities and HTA bodies.

Reference

1. Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler H-G, Kristensen FB. Improving the contribution of regulatory assessment reports to health technology assessments – a collaboration between the European Medicines Agency and the European Network for Health Technology Assessment. Value Health 2014;17(5):634–41.

Management Board delays formal adoption of European Medicines Agency publication of clinical-trial-data policy to October 2014

9 July 2014 – The Management Board of the European Medicines Agency (EMA) has postponed formal adoption of the policy on publication of clinical trial data to its 2 October 2014 meeting. Further clarifications on wording and practical arrangements will be discussed by Board members, who have confirmed their general support to the overall aims and objectives of the policy, including the more user-friendly amendments proposed by EMA Executive Director Guido Rasi that would allow data to be downloaded, saved, or printed for academic and non-commercial research purposes.

Further to the agreement reached with the European Commission in accordance with Article 80 of Regulation (EC) No 726/2004, the Board was not able to conclude on the final wording of the policy through a written procedure. Members of the Board have offered additional valuable contributions which will now be considered and addressed in the next few weeks, with a view to reaching final agreement at the next Management Board meeting in October.

The Agency welcomes this additional round of joint reflections and respects all opinions, as well as the views expressed by several Member States, which largely reproduce the complexity of the debate on both political and technical aspects which have emerged during the previous general and more targeted consultation phases. In the last 12 months, the Agency has attempted to strike a balance between proactive data disclosure, the absolute need to protect personal data, and the concerns relating to the protection of commercially confidential information.

The Agency management remains committed to introducing this additional measure towards transparency as soon as possible, so as to enhance citizens' awareness and confidence in the EU authorisation system for medicinal products. The Agency has also underlined several times that the new policy, if approved, will be without prejudice to the provisions of Regulation (EC) No 1049/2001 on access to documents and the new clinical trial Regulation (EC) No 536/2014, which will become applicable in 2016 at the earliest and, as also noted during the debate, will apply to clinical trials conducted in the European Union.

The Agency management is conscious that any delay prevents citizens, and in particular academics and non-commercial researchers, from enjoying the benefits of proactive publication of clinical trial data for a further period. The Agency will continue to work with the Management Board and the European Commission ahead of the 2 October meeting to ensure that members receive the clarifications requested and to facilitate the adoption of the policy.

Guide on methodological standards in pharmacoepidemiology revised to include pharmacogenetic studies

14 July 2014 – The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), coordinated by the European Medicines

Agency, has revised its guide on methodological standards in pharmacoepidemiology and added a chapter on the design and analysis of pharmacogenetic studies.

These studies aim to investigate how individual genetic variations determine the response to a medicine, both in terms of therapeutic effect and adverse drug reactions. They help optimise the prediction of treatment response leading to a better use of medicines.

The new chapter on pharmacogenetic studies provides a comprehensive overview of all relevant methodological guidance for the conduct of pharmacogenetic studies, from the identification of genetic variants through to study design, data collection, analysis, and reporting.

Like the other sections of the guide, this chapter contains web links to internationally agreed recommendations and key points from important guidelines, published articles, and textbooks. It also highlights good practice guidance for the conduct of these studies.

ENCePP is a network of over 170 research centres, existing networks, and providers of healthcare data, whose aim is to strengthen the post-authorisation monitoring of medicines by facilitating the conduct of multicentre, independent, and scientifically robust studies focusing on the safety and balance of benefits and risks.

By offering a single and comprehensive overview of all relevant methodological guidance for researchers in pharmacoepidemiology and pharmacovigilance, the ENCePP guide is a key tool in supporting high-quality post-authorisation studies.

Users can view the guide as HMTL webpages with links to each chapter and section and also as a consolidated PDF version for download.

The guide is updated annually to ensure that all developments in the field are incorporated.