# News from the EMA

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## Adaptive pathways: a future approach to bring new medicines to patients?

December 12, 2015 – "Adaptive pathways should be the preferred approach in the near future to bring new medicines to patients." A number of scientists, including members of the European Medicines Agency (EMA) and its scientific Committees take this position in a co-authored article published in Clinical Pharmacology and Therapeutics.

The concept of adaptive pathways foresees an early approval of a medicine for a restricted patient population based on small initial clinical studies. The first approval is followed by progressive adaptations of the marketing authorisation to expand access to the medicine to broader patient populations based on data gathered from its use and additional studies.

Under the header 'From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients,' the authors, who are part of the New Drug Development Paradigm (NEWDIGS) initiative, analyse the key drivers of adaptive licensing. These include:

- The patients' demand for timely access to medicines, in particular where there are unmet medical needs. With adaptive licensing, new treatments would be made available to some patients earlier, on a smaller evidence base, if efficacy has been observed in this patient population.
- A better understanding of pathologies which has led to the identification of subgroups of patients who are likely to better respond to certain medicines than others. For many of these subgroups, a progressive approach to licensing while learning from real-world experience may become the only viable access route to new treatments.
- The growing financial pressure on healthcare systems and a call for a more targeted use of medicines to increase their therapeutic value.
- The pressure on industry to make the development of medicines, in particular for chronic diseases, sustainable. Development programs targeting smaller, better defined populations would lower the threshold for financing a drug's development and allow for more medicines to be brought forward.

A number of recent developments are fostering the transition from a traditional approach, which implies large trials and a marketing authorisation for broad groups of patients, to an adaptive approach. These include the development of innovative clinical trial designs, learning healthcare systems and the inclusion of patients in decision-making processes to better understand what level of uncertainty they are willing to accept.

### *EMA adaptive pathways pilot project*

EMA launched a pilot project on adaptive pathways (formerly known as adaptive licensing) in March 2014 to explore this approach with real medicines in development.

As of November 2014, the Agency had received and assessed 29 applications as part of the pilot, nine of which had been selected for discussion with the applicant.

Stage I of the pilot project will close at the end of February 2015. The Agency will then focus on stage II of the project. This will include in-depth, face-to-face meetings with the applicants for the applications selected.

After 28 February 2015, EMA will still consider new applications for stage II face-to-face meetings if they are well-developed. Applicants are invited to contact EMA at adaptivepathways@ema.europa.eu for advice on the content and suitability of their request to be considered for stage II of the pilot.

EMA is planning to publish a report on initial experience gained as part of the pilot project by the end of 2014.



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EMA recently changed the name of its pilot project from adaptive licensing to adaptive pathways to better reflect the idea of a life-span approach to bring new medicines to patients with clinical drug development, licensing, reimbursement, and utilisation in clinical practice, and monitoring viewed as a continuum.

## Europe to boost international cooperation on generics

January 19, 2015 – The European Medicines Agency (EMA) is ready to share its assessments of applications for generic medicines in real time with collaborating regulatory agencies outside the European Union (EU). This initiative aims to facilitate the timely authorisation and availability of safe, effective and high quality generic medicines worldwide.

The information-sharing initiative is part of the International Generic Drug Regulators Pilot (IGDRP). It started in July 2014 using the European Union decentralised procedure as a model, and it is now extended to the centralised procedure.

The EU is leading this initiative with the aim to both save global assessment resources and to facilitate and strengthen the scientific assessment process for medicines. It is expected that this sharing of assessments will allow authorisation of generic products in concerned countries in a coordinated and resource effective way.

The first phase of the pilot project will involve the EU, Australia, Canada, Chinese Taipei and Switzerland. Other members of the IGDRP may decide to take part in the pilot programme at a later stage. These include Brazil, China, Japan, Korea, Mexico, New Zealand, Russia, Singapore and South Africa. The European Directorate for the Quality of Medicines & Healthcare (EDQM) and the World Health Organization (WHO) participate to IGDRP as observers.

In the initial phase, 10 applications for generic medicines will be selected for participation in the pilot; further products might be considered after evaluation of first results.

Companies are invited to express their interest in participating in the pilot programme. Further information has been published today on the EMA website.

*About IGDRP*

The IGDRP was launched in April 2012 to strengthen collaboration and convergence between regulatory agencies worldwide and mitigate challenges of global generic development and approval programs.

This information-sharing initiative is one of the work packages of the IGDRP. The EU is also involved in other areas of cooperation which aim to explore work sharing possibilities in the area of active substance master file, inspection of sites conducting bioequivalence and bio-analytical studies and information sharing on pharmaceutical quality issues.

## Regulatory information - Paediatric guidance revised to reflect changes to European Commission guideline

January 21, 2015 – The European Medicines Agency has published revised documentation related to paediatric investigation plans (PIPs) to reflect recent changes to the European Commission's guideline on PIPs. The guidance documents relate to the procedures for submission of PIP/waiver applications, re-examination and compliance check.

The revised documents take into account the changes and simplifications that have been introduced by the European Commission in the recently published guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies.

## New international standard to improve safety of medicines

January 21, 2015 – The European Medicines Agency (EMA) has published a guide to support the implementation of a new international standard for the safety monitoring of medicines in the European Union (EU). The so-called ISO ICSR standard improves the reporting of suspected side effects of medicines in Individual Case Safety Reports (ICSRs). The use of the new international standard will take effect on 1 July 2016.

ISO ICSR aims to establish the same format for the reports on individual cases of suspected side effects in patients due to a medicine across the world. It also is expected to include better information on medicines that might be associated with an adverse drug reaction and on the therapeutic uses of those medicines. In addition, the standard also strengthens personal data protection in the records of ICSRs collected by pharmaceutical companies and regulatory authorities.

This will improve the quality of data collected, and increase the ability to search and analyse them. Regulatory authorities will be able to detect

and address safety issues with medicines more quickly, and therefore better protect patients.

The new guide developed jointly by EMA and the Heads of Medicines Agencies (HMA) will be of interest to pharmaceutical companies and medicines regulatory authorities in EU Member States and will support them to prepare for the use of the standard. The guide specifically defines the electronic transmission process of ICSRs, the format and content of the ICSR, the business rules for report validation as well as classification and data quality principles. It will also assist software providers and IT developers as pharmacovigilance databases are being developed.

The finalisation of the guide is a major step in EMA's preparation for an enhanced EudraVigilance system, the European database of all suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA), as required by the EU pharmacovigilance legislation.

Notes:

- This guide is based on the ICH E2B (R3) guideline and the corresponding ISO ICSR standard as referred to in Article 26 of the Commission Implementing Regulation (EU) No. 520/2012. The guide will apply with the use of the ISO ICSR standard as of 1 July 2016.
- The next step for the development of the EudraVigilance system based on the new ISO ICSR standard and related EU guide are further outlined in the News bulletin for pharmacovigilance programme update - Issue 2.

## Public consultation on application of transparency rules of EU Clinical Trial Regulation

January 21, 2015 – The public consultation on how the transparency rules of the European Clinical Trial Regulation will be applied in the new clinical trial database is launched by the European Medicines Agency (EMA) today. Stakeholders are invited to send their comments before 18 February 2015.

The European Clinical Trial Regulation aims to create an environment that is favourable to conducting clinical trials in the European Union (EU), with the highest standards of safety for participants. The Regulation ensures that the rules for conducting clinical trials are consistent throughout the EU. It also transforms the level of information publicly available for each clinical trial carried out in the EU by requiring transparency on the authorisation, conduct, and results of the trial. The Regulation will apply to clinical trials that are registered once the Regulation is in operation (not before 28 May 2016).

The key instrument to deal with clinical trials in a transparent way is the new clinical trial portal and database. It will be used for submission and maintenance of clinical trial applications and authorisations within the EU. It will serve as the source of public information on the clinical trial applications assessed, and all clinical trials conducted in the EU. According to the Regulation, EMA is responsible for the development and maintenance of the portal and database, while the authorisation and oversight of clinical trials will remain with the EU Member States.

The public will be able to access extensive details of each trial including the major characteristics of the trial, the start and end of recruitment, end date of the trial and substantial modifications to the trial. These details will be made public as they occur starting with the decision on the trial. A summary of results and lay summary will be published 12 months after the end of the trial. For those trials included in a marketing authorisation application in the EU, clinical study reports will also be published 30 days after the procedure for granting the marketing authorisation has been completed or the application has been withdrawn.

The Regulation requires that the clinical trial database shall be publicly available unless one or more of the following exceptions apply:

- protection of personal data;
- protection of commercially confidential information, in particular taking into account the marketing authorisation status of the medicine, unless there is an overriding public interest;
- protection of confidential communication between Member States in the preparation of their assessment;
- protection of the supervision of clinical trials by Member States.

The document under consultation sets out proposals for the application of the transparency rules of the European Clinical Trial Regulation for stakeholders to review and comment on. The proposals aim to balance the right of patients and the public to access extensive and timely information on clinical trials, and developers' and researchers' need to benefit from investments. This will support the EU as a suitable location for

innovative, cutting-edge research and development of medicines.

*How is this public consultation linked to EMA's policy on the publication of clinical data?*

This public consultation refers only to the practical application of transparency rules for the clinical trial portal and database that is established within the European Clinical Trial Regulation. The European Clinical Trial Regulation is distinct from EMA's policy on the publication of clinical data, which has already come into force (January 2015). There are several important differences between the provisions of the European Clinical Trial Regulation and EMA's policy. Under EMA's policy, the Agency proactively publishes the clinical study reports submitted as part of marketing-authorisation applications for human medicines.This means that the policy applies to clinical reports of studies that are beyond the scope of the European Clinical Trial Regulation as it, for example, also includes clinical trials that are conducted outside the EU but submitted to EMA for marketing authorisation in Europe.

Note:

- The Clinical Trial Regulation EU No. 536/2014 requires that the Agency develops and maintains the clinical trial portal and database to act as a single portal for submission and maintenance of clinical trial applications and authorisations within the EU, to support the coordinated assessment and exchange of information between Member States on the processes of authorisation and supervision of clinical trials, and to serve as the source of public information on clinical trial applications assessed, and clinical trials conducted in the EU, from the time of decision on each trial up to the inclusion of the results of those trials.

## Regulatory information - Transitioning to mandatory use of electronic application forms

February 5, 2015 – The European Medicines Agency (EMA) is announcing the transition to the mandatory use of electronic application forms for initial marketing authorisations, variations and renewals for human and veterinary medicines.

As of 1 July 2015 it will be mandatory for companies submitting applications for centralised procedures to use the electronic application form.

From 1 January 2016 the application forms in Word format published by the European Commission will no longer be available and only the latest version of the electronic application form will be used for all EU procedures, including national procedures.

The electronic application forms offer a convenient, online version of the currently used paper versions, which are published and maintained on the European Commission's EudraLex website. These electronic forms are designed to reflect and capture the same content as the paper-based application forms. EMA first made these forms available to companies in July 2012, following a successful pilot phase. Since the initial release, the forms have been significantly improved and a further release based on change requests will be made available this Spring.

The mandatory use of these forms is expected to reduce the administrative burden for both the regulatory authorities and the industry, while at the same time improving data quality and consistency during data entry.

Further information on the new requirements can be found on the eSubmission website where an information leaflet on the mandatory use of the forms has been published.

## Regulatory information - EMA introduces weekly start dates for the assessment of type II variations from March 2015

February 20, 2015 – Starting March 2015, the European Medicines Agency introduced weekly start dates to facilitate the assessment of certain type II and worksharing variation applications for medicines for human use. These changes are one of the outcomes of the Agency's structural reorganisation which was initiated in September 2013 to improve the efficiency and effectiveness of its operations. They are expected to offer more flexibility to applicants and streamline the assessment of applications by allowing certain variations to conclude outside of the plenary meeting of the Committee for Medicinal Products for Human Use (CHMP).

The new process will be applicable to most type II including grouped and worksharing variations. For these variations, companies will be able to send their applications to the Agency according to the weekly submission slots and the assessment will start on a weekly basis. The CHMP will adopt its scientific opinion at different time points either outside the CHMP meeting or at the meeting, depending on the start date of the review.

Assessment of responses to requests for supplementary information will also follow the weekly-start timetables.

The validation period between submission and procedure start as well as the assessment timelines as provided for in the legislation will remain unchanged. Linguistic review of product information changes for these variations will continue to follow the monthly review cycle starting five days after the CHMP monthly plenary meeting.

The new process will not apply to variations for which amendment of the marketing authorisation by the European Commission is required within two months from CHMP opinion. Similarly, it will not apply to variations involving the Pharmacovigilance and Risk Assessment Committee (PRAC) or the Committee for Advanced Therapies (CAT) either. These variations will continue to follow the existing monthly-start timetables.

Further details can be found in the post-authorisation guidance on type II variations which has been revised to reflect these changes. The new weekly-start timetables have also been published on the Agency's website.