



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

3 September 2018  
EMA/365499/2018  
Human Medicines Research and Development Support Division

## Highlight report of the 3<sup>rd</sup> Industry stakeholder platform on research and development support

18 May 2018

Role	Name
Chair:	Michael Berntgen
Present:	<p><b>Industry:</b> <b>AESGP</b> Chitkala Kalidas, <b>EBE:</b> Claudia Dollins, Mats Ericson, Anja Langeneckert, Olaf Mengels, Fiona Reekie, <b>EFPIA:</b> Adam Heathfield, Angelika Joos, Jan Vindberg-Larsen, Genevieve Le Visage, Isabelle Stöckert, Pär Tellner, Chris Walker, Danuta Wawrzak (Topic 4 only), <b>EUCOPE:</b> James Barnes, Jill Morrell, Patrizia Nestby, Lars Hyeled-Nielsen, Martine Zimmermann, <b>EuropaBio:</b> Christiane Abouzeid, Simon Bennett, Emma Du Four, Alexa Hunter, David King, Niklaus Wagner, <b>Medicines for Europe:</b> Rina Joshi, Beata Stepniewska, <b>Vaccines Europe:</b> Virginia Acha, Kandeepan Ganeshalingam, Susanne Heiland-Kunath, Muriel Pasté, Solange Corriol-Rohou, Claire Hill-Venning</p> <p><b>EMA:</b> Enrica Alteri, Michael Berntgen, Ralph Bax, Sylvie Beausuroy, Alison Cave, Francesca Cerreta, Robert Coggins, Corinne De Vries, Falk Ehmann, Lise Flaunø, Zahra Hanaizi, Kristina Larsson, Jordi Llinares, Dirk Mentzer, Jane Moseley, Marisa Papaluca, Francesco Pignatti, Marie Helene Pinheiro, Armin Ritzhaupt, Tomas Salmonson, Alexios Skarlatos, Enrico Tognana, Paolo Tomasi, Spiros Vamvakas</p> <p><b>Other:</b> Petra Zoellner (Medtech Europe), Cláudia Furtado (INFARMED), Ingvil von Mehren Sæterdal (NIPH), Wytse Bruinsma (ZIN), Ad Schuurman (ZIN), Niels Speksnijder (ZIN)</p>

This was the third event in a series of regular meetings between regulators and representatives of industry stakeholder organisations to address all areas of product development support, from scientific advice, over specifics for paediatric and orphan medicines and to innovation support. The aim of the platform is to provide an opportunity for both general updates and more focused discussions on specific processes or issues to support continuous improvement, and generally to foster a constructive dialogue with industry stakeholders.



## **Exchange on experience with the implementation of the Orphan notice**

EMA gave an overview of the experience so far with some of the key elements which were introduced and clarified with the Notice. The discussion focused on the reassessment of orphan criteria in the context of an extension of an indication within an already authorised orphan condition.

From an industry perspective there are challenges regarding the interpretation of ‘same condition’ in such extensions and the future implications for label modifications. It was voiced that the revision in the Notice could have significant impact on research and business models, contradicting spirit of the orphan legislation, and hampering orphan drug development and innovation in Europe. As a result industry considered that this requirement may limit the development, and further extensions, of treatments for rare diseases due to increased regulatory uncertainty, create additional regulatory hurdles in the EU compared to other global regulators, and potentially shift companies’ R&D focus to non-rare therapeutic diseases. However, at this point in time there is only very limited experience with the reassessment at extension of an indication. EMA is tracking all products affected by the reassessment and further discussions are recommended when more experience has been gained.

Industry also voiced the need for clarity about the grounds on which basis the reassessment is done as well as practical guidance on what should be submitted for the maintenance report were voiced. EMA explained that no reassessment is done on extensions to different age groups, or to extensions into a “new” target population (within the same condition) where no other medicinal products are approved. The already authorised indication for the product (for which an assessment has already been done) is not revisited, it is only the new extended indication which is considered. A reassessment is needed if the target patient population is broadened (within the orphan condition) e.g. to a new line of treatment or a new subgroup (severity, biomarker, mutations etc.).

Once the decision on a reassessment has been taken the same procedure as for as for initial maintenance applies and the same type of information is required from the applicant. Similar timelines are followed and the same depth of assessment is done by COMP (e.g. when establishing significant benefit over all authorised products). This ensures consistency and predictability for applicant as well as the COMP.

EMA highlighted that Protocol Assistance can be requested for extension studies as well and this should be considered by developers more frequently as currently only limited questions on significant benefit relating to extension of indications within an orphan condition are being raised.

### **FOLLOW-UP:**

- Communication and cascading of experience with the application of the Notice so far and the criteria applied for the review of extension of indications, including particular outreach to SMEs
- Follow-up review of the application of the Notice for extensions of indications, by both EMA and industry

## **Targeting “histology-independent indications” and resulting challenges in the context of orphan designations**

Several products aiming for an histology-independent indication are in the pipeline. In this context, developers working in the area of rare diseases raised the issue that incentives available in the EU for tissue specific therapies are currently not available for tissue agnostic/histology-independent therapies targeting oncogenic drivers with low prevalence. Furthermore, due to low prevalence of patients per tumour type and high testing burden involved it is not feasible to enrol every single type of tumour

that harbours the biomarker in one clinical trial with adequate number of patients. Histology-independent development in rare conditions as well as rare biomarker subsets of common conditions inherently involve extrapolation of data from representative tumour types to the overall population with the same specific biomarker/oncogenic driver.

Industry highlighted that the current EU regulatory framework for Orphan drugs relies on traditional site and histology definition of diseases. While there may be a path for orphan drug designation (ODD) for biomarker selected rare sub-populations in non-rare conditions, the path to ODD for a biomarker selected histology-independent indication in rare disease is not yet defined. This could pose a barrier to drug developers working in areas of high unmet medical need and may delay progress in innovation. If the same principle needs to be proven separately for each tumour type, this would lead to a complex life cycle management and delays access to patients who could benefit from the treatment.

EMA presented the current thinking on this topic. In principle, there are no regulatory or scientific objections to histology-independent indications and the concept is already contemplated in the anticancer guideline. However, in practice, the concept is still challenging. There is currently a lack of successful examples of marketing authorisation applications in the EU but on the other hand there is growing experience from scientific advices. There are ongoing reflections at the level of oncology and biostatistics working parties, and a guidance possibly to be drafted.

From the orphan designation perspective the challenges were also clarified: The orphan condition has to fit the regulatory context and may not match a therapeutic indication in a non-orphan regulatory setting. COMP does not define new conditions to serve the regulation or the development of a specific product but relies on established terminology and classifications. From the EU orphan perspective there are still several unanswered questions which would need a broader discussion across regulators, developers as well as academia:

- How to define a histology independent condition to reflect a “disease”?
  - Alternatively, designate all underlying cancers + biomarker subsets.
- If this was overcome, how justify significant benefit?
  - many products would likely be approved for the patients
  - but not the same product for across histologies
- How to establish the natural history of the histology independent condition?

#### **FOLLOW-UP:**

- Follow up on the discussions by the Oncology WP and Biostatistics WP including potential opportunities to engage with stakeholders
- Sponsors to consider putting forward proposals for development plans in histology-independent indication in the context of the development support activities, outlining the challenges they are facing

### **Introduction to the upcoming rollout of the new technology to support orphan designation procedures**

As a follow-up to the previous platform meeting, EMA presented the new submission portal for orphan designation applications that will be launched in mid-June. The portal provides a single space where applicants can submit and manage the information and documents related to their applications for

orphan designation. This is expected to reduce the time needed to prepare and submit the applications. During the review process, applicants can check the status of their applications from any device and receive automatic notifications when the status of the application changes.

The new portal is part of a longer-term programme that aims to make the handling of product-related applications easier and utilises the domains of master data in pharmaceutical regulatory processes (SPOR). After its launch applicants will still be able to use the existing submission process for a short transition period however, the Agency strongly encourages companies to start using the new portal once it is available online.

Representatives from industry who took part in the user testing provided their experience, which will be taken into account for the refinement of the portal ahead of its launch. EMA reported that volunteers from 26 different organisations took part in the testing, which showed high levels of satisfaction.

#### **FOLLOW-UP:**

- Industry to cascade information on this new operational environment within their networks to raise awareness and allow for implementation preparation
- Roll-out of training opportunities for sponsors and communication material

### **Experience with the review of digital technology proposals in medicine development programmes**

Industry presented a perspective on the application of digital technology to support transformation of drug development and regulation of new therapeutic solutions. The scope and definition is broad, ranging in terms of data from data generation to data analytics, in terms of technology from artificial intelligence to robotics, and in terms of tools from mobile monitoring devices to virtual reality. The digital ecosystem will connect in multiple ways with healthcare systems. With regard to medicines regulation, this is expected to lead to greater personalisation, evolving evidence generation, decision making based on data evolution, new “types” of products, as well as a shift in skills and approaches. Once a product is on the market areas like safety evidence, patient communication and post-licensing evidence generation will be impacted.

EMA provided feedback on the experience gained through the engagement in qualification of novel methodologies, product-related scientific advice as well as discussions in the Innovation Task Force. The Agency is interested to support the use of these technologies in the development of medicinal products; in this space developers need to consider the different remits from different decision makers. Early engagement is essential, particularly if it is envisaged to have significant reliance on these technologies for regulatory decision-making, or if input from different stakeholders needs to be sought. To facilitate obtaining regulatory input, questions to the EMA should be framed within a medicine development viewpoint (e.g. clinical relevance, GXP inspectability, sensitivity and specificity, where applicable).

#### **FOLLOW-UP:**

- Opportunity for additional experience gain through engagement by sponsors in development proposals / qualification of novel methodologies
- Engagement in ongoing initiatives, like work on big data as well as the workshop on medical information

## **Evolving framework for the co-development of medicinal products with companion diagnostics**

This topic was discussed at the first R&D industry stakeholder meeting in April 2017 and was an opportunity to follow-up on actions identified at the time. With the publication of the new medical device and in vitro diagnostic regulations in May 2017, EMA has conducted an impact assessment and drafted an implementation plan. In November 2017, the Competent Authority on Medical Devices (CAMD) published a road map for the implementation of the new device regulations and EMA is identified as one of the responsible working parties on companion diagnostics. As part of the implementation, EMA is already working with EC working groups ('In Vitro Diagnostic Technical Group (IVD TG) and Clinical Investigation and Evaluation Working Group (CIE WG)) and other responsible parties to discuss concepts of clinical performance studies relevant for both companion diagnostic and medicinal product evaluation as well as to discuss interactions with Notified Bodies. It was reported that such a multistakeholder dialogue was organised by IVD TG and CIE WG in February 2018. Progress was also reported on the concept paper on predictive biomarker testing which was released for public consultation in July 2017 and for which 100 pages of comments were received on aspects related to data requirements for analytical validation, clinical performance studies and on the future interaction and consultation process between EMA and NBs. A meeting to discuss these comments with representation from involved stakeholders was organised in June 2018.

Topics addressed by Industry revolved around the roles and responsibilities for the companion diagnostic consultation and evaluation process, the requirement for procedural guidance, clinical performance, investigational use in clinical trials, labelling and novel/complex technologies. It was understood that these are important topics to resolve well before the new regulation will apply. It is understood by all parties that this is a complex area involving many different stakeholders and that due to the complexity, there is a need to continue dialogue and interaction among all involved stakeholders. All agreed that the expert meeting in June was an excellent opportunity on which to build for further interaction.

### **FOLLOW-UP:**

- Detailed discussions at the upcoming expert workshop on 18 June 2018 together with all stakeholders
- Explore ways to communicate oversight and progress of implementation activities and timelines

## **Understanding which technologies are coming into the healthcare systems**

In a joint presentation by EMA, EUnetHTA and payer representatives the topic of horizon scanning was newly introduced to the platform. Different elements are taken into consideration for the approach to horizon scanning: objectives / desired impact; scope of technologies / interventions; observation period ("distance to horizon"); data sources and detection methodology; triage; reporting mechanisms. It was noted that decision makers use different methodologies and for various purposes. Collaboration across decision makers in this space stems from the HTA Network Reflection Paper on ["Synergies between regulatory and HTA issues on pharmaceuticals"](#), the [EMA-EUnetHTA work plan 2017-2020](#) as well as the outcome of the [EMA – Payer Community meeting](#). Opportunities for such collaboration can be organised in three areas: 1/ Products under regulatory assessment; 2/ Products to be submitted for assessment by decision makers; 3/ The wider horizon – products in development and beyond. In this context it was raised how increased cooperation across decision makers can streamline and support requests to industry for provision of data in support of different horizon scanning activities, how to

make certain data fields concerning ongoing / planned submissions (like applied indication, ATC code and name of applicant) available to other decision makers, and how platforms such as EMA business pipeline meetings can also involve HTAs and payers to be mutually beneficial.

Acknowledging the relevance and importance of this topic in terms of preparedness and the efficient decision making for introducing innovation into healthcare systems, industry raised the need for clear roles and responsibilities with clarity of data to be shared. Opportunities for business pipeline meetings with multiple decision makers can be considered on a voluntary basis. Other alternatives are strategic forums where products discussions are held and information can be exchanged. EMA, EUnetHTA and payers will take this input into consideration for the follow-up developments.

#### **FOLLOW-UP:**

- Development of the items / data fields subject to the sharing of information between regulators, HTAs and payers to support horizon scanning activities
- Possibility for expand the existing platform of EMA business pipeline meetings to also include HTAs and payers
- From EUnetHTA: invitation to sponsors to make proposals for submission to WP4 / joint REA production

#### **Focus group “Post-licensing evidence generation” (PLEG)**

EMA provided feedback from the first meeting of the PLEG focus group. This focus group was set up as an outcome of the 2<sup>nd</sup> R&D industry stakeholder platform meeting with the objectives as follows:

- To identify issues and barriers to seeking scientific advice (SA) on PLEG, and discuss potential solutions, starting from an output outlining what comprises PLEG.
- To discuss several key areas in the context of seeking scientific advice on PLEG including approaches for questions on which scientific advice is sought, along with the appropriate structure of a company position, and types of products where such early engagement on PLEG would be particularly relevant, including optimum timing and opportunities in “Late” parallel consultation.

The group is composed of nominees from industry associations, EUnetHTA and EMA. The aim of the focus group is to deliver recommendations via a short document on how/when considering scientific advice/dialogue/consultation for PLEG to serve as a discussion tool/decision aid. The concept for the high-level content of the document was presented. The focus group considered that PLEG advice should be seen in the context of a continuum of evidence generation rather as separate pre- and post-licensing. Regarding issues or barriers to seeking SA on PLEG, and experience on the types of uncertainties and data requests by regulators and HTAs, collection of feedback from industry and views of EMA and HTAs will be sought, and appropriate methods to do so are under discussion within the group.

In summary, good progress is being made within the group with regard to the objectives. Industry echoed that the output of the group will provide key considerations for best use of advice to help plan for effective post licensing evidence generation. Further feedback to the R&D stakeholder platform will be made with the availability of a mature draft output expected in Q3/4 2018.

#### **FOLLOW-UP:**

- Report at the next platform meeting about the output of the focus group

## Follow-up from the EC/EMA workshop on paediatrics

EMA provided feedback from the EC/EMA multi stakeholder workshop held in March 2018, which followed the publication of the EC 10-year report on the Paediatric Regulation in November 2017 with the aim of developing an action plan to improve the implementation of the paediatric regulation. Representatives of all relevant stakeholders participated at the workshop to discuss mainly the following topics:

1. Identifying paediatric medical needs (methodology)
2. Ensuring timely completion of PIPs
3. Improving the handling of PIP applications
4. Strengthening of international cooperation between regulators
5. Increasing transparency around paediatric medicines

Further details can be found in the published [report](#) on this workshop.

EMA also discussed recent developments regarding the organisation of the PDCO meeting in August which will be aligned to the practice of the other committees in order to support the possibilities for scientific exchange during the meetings, specifically with the CHMP. Therefore, as announced beginning of the year, the timelines for submissions have been amended in order to allow for a written procedure in August and at the same time ensuring all possibilities for a scientific discussion of the paediatric procedures.

The representatives from industry provided reflections on the workshop and their priorities. These included having a common definition and agreement on paediatric needs by all stakeholders, the increased use of innovative approaches for study design and/or data collection, sufficient infrastructure for the conduct of clinical trials in children and a better alignment of national procedures. The main focus at this meeting, however, was on a 'pragmatic approach to PIP preparation and agreement, to include more dialogue and input from other stakeholders'. This includes improved communication opportunities during the PIP process learning for example from other regulatory procedures and working on a simplification of the documentation needed. For the pragmatic approach it was proposed to guide the PIP process by the course of development of medicinal products in general, i.e. to agree a PIP based on available data at that time integrating a timeline of development milestones. This would be particularly useful in cases where modelling and simulation and extrapolation measures are used.

In order to support the further development in these topics, industry representatives provided an overview of concrete actions and also that a working group had been appointed to elaborate on the concept of PIP development based on evolution of data and appropriate scientific content and documentation.

### FOLLOW-UP:

- The [report](#) on the EC/EMA workshop in March 2018 has been published together with a video from the workshop and an infographic (see on [Paediatric medicines: Overview](#))
- Publication of the EC/EMA action plan as a follow-up to the workshop in March 2018

## Update on PRIME

EMA presented highlights of its recently published [2-year overview report](#) and updated guidance and Q&A published based on its experience to date.

Detailed results of a survey conducted with PRIME applicants on the kick-off meetings were presented. This survey highlighted an overall good satisfaction with this type of meeting, including its preparatory steps, objectives and impact it has on the products' development plans. The survey also highlighted the need to improve on the support provided to applicants to better understand how to interact with different Committees and the follow-up actions after the meeting. As a first step, a new Guidance on interactions in the context of PRIME has been published and the Agency will continue to improve on areas identified.

**FOLLOW-UP:**

- Follow-up on the findings from the recent survey