10 January 2019
EMA/845782/2018
Human Medicines Research and Development Support Division

Highlight report of the 4th Industry stakeholder platform on research and development support

23 November 2018

Role	Name
Chair:	Michael Berntgen
Present:	Industry: **AESGP** Andrew Thornley. **EBE** Mats Ericson, Anja Langeneckert, Mireille Muller, Claudia Dollins, David Ribeiro, Fiona Reekie, Sonja Pumpluen. **EFPIA** Sini Eskola, Scott Askin, Geneviève Le Visage, Isabelle Stoeckert, Sabine Atzor, Susan Longmann, Catherine Weil, David Jefferys. **EUCOPE** Angelika Joos, Joao Duarte, Jill Morrell, Lucia D'Apote, Dot Bruce, Maren von Fritschen, Lars Hyveled-Nielsen. **EuropaBio** Simon Bennett, Alexa Hunter, David King, Emma Du Four, Christiane Abouzeid. **Medicines for Europe** Anabela Godinho, Susana Almeida. **Vaccines Europe** Adam Heathfield, Solange Corriol-Rohou, Muriel Pasté, Virginia Acha. EMA: Enrica Alteri, Armin Ritzhaupt, Ivana Hayes, Francesca Cerreta, Falk Ehmann, Francesco Pignatti, Spiros Vamvakas, Frank Petavy, Jane Moseley, Kristina Larsson, Laura Liebers, Chrissi Pallidis, Gunter Egger, Ralph Bax, Marlena Zarnecka, Zigmars Sebris, Kevin Cunningham, Corinne de Vries, Peter Arlett, Xavier Kurz, Marie Helene Pinheiro, Leonor Enes, Helene Casaert, Andersson Anita. EMA scientific committees and working parties: Dirk Menzer, Koen Norga, Violeta Stoyanova-Beninska, Pierre Demolis. Other: Sacha Wissink, Nadja Heimonen, Debbie Mackenzie, Fabrice Marsicano, Chitkala Kalidas, Heidi Kern, Silvia Garcia, Anthony Compton, Claudia Hey (EFPIA), Fabio D'Atri (EC), Dario Pirovano, Michael Strubin (Medtech Europe), Chantal Guilhaume, Maggie Galbraith (EUnetHTA).

This was the fourth 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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

specific processes or issues to support continuous improvement, and generally to foster a constructive dialogue with industry stakeholders.

Exchange on the practical considerations for the future regulation of integrated drug-device combinations

The discussion focused on the implementation of Article 117 of the medical devices regulation that makes changes to how medicinal products with integral device components are regulated. EMA reported on the progress for the guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product developed by the quality and biologics working parties (QWP and BWP). The guideline's main focus will be on dossier requirements for regulatory submissions (Module 3) but also covers aspects related to implementation of Article 117. To facilitate development of the guideline, EMA and the QWP/BWP drafting group are in dialogue with representatives of Notified Bodies to understand each other's roles in the review of the medical device part of a combination product. The drafting group anticipates a publication of the draft guideline in Q2 2019 with a 6 month public consultation. EMA also announced that a new Q&A will be published to answer procedural and regulatory questions in relation to implementation of the new medical devices and IVD regulations. The first draft of the Q&A will focus on critical questions for implementation of Article 117, i.e. when Article 117 applies, if it applies for currently marketed products, if it will apply for post-authorisation changes to the device and when the notified body opinion should be submitted. The draft Q&A has been shared with the European Commission and Member States and once feedback is received, publication is anticipated by early Q1 2019.

Topics addressed revolved around the roles and responsibilities of the EMA and notified bodies for medicinal products with an integral device and the expectations for clinical evidence, labelling and instructions for use, QMS vs GMP, and scientific advice under the new regulations. Industry also expressed a need for regulators to develop a contingency plan should there be notified body capacity issues. It is understood by all parties that this is a challenging area involving many different stakeholders and there is a need to continue dialogue and interaction to ensure a collaborative approach to implementation of Art. 117 across industry, regulators and notified bodies.

FOLLOW-UP:

- Finalisation of the scientific quality guideline for public consultation by Q2, 2019 and the procedural/regulatory Q&A by EMA and publication expected by January 2019
- Additional information to be provided by trade associations in terms of numbers and types of devices, for initial MAAs and post-authorisation submissions for products in the centralised and decentralised system including additional reach-out to other trade associations
- Further continuous engagement/dialogue with the other stakeholders in relevant fora to enable further discussion on scientific (e.g. specific evidence requirements) and operational elements (e.g. contingency planning)

Follow-up on experience with digital technology proposals in medicine development programmes

Regulatory challenges of using digital tools in clinical development were presented from an industry perspective. With the aim to leverage technologies to build smarter clinical trials around patients and the evolving regulatory landscape in developing digital tools in EU, the drive to develop eHealth, the

need to clarify expectations on data, and diversity in guidance and regulation are considered challenging. Qualification of digital technologies could be a useful tool provided the process is addressing the time-constrains during development. Several digital technologies have been subject to qualifications over the past years; the eSource Qualification experience was rehearsed as case study. Learnings from this experience included the positive level of engagement by regulators and the interactions held. The process would benefit from additional guidance.

EMA complemented this review with a summary of considerations for successful qualification proposals for digital technologies. This is based on experience with qualifications for e.g. the development of novel outcome measures, scientific advices and ITF meetings on adherence / appropriate medication, as well as participation to IMI initiatives. An early regulatory engagement is essential if the later application will be heavily reliant on such data.

Acknowledging the importance of these discussions and the relevance of digital technologies in a fast-paced development space, it was agreed to deepen the conversation on how to obtain qualification advice on digital technologies, in order to stimulate more such engagement.

FOLLOW-UP:

- Foster the use of qualification procedures for establishing digital technologies to support medicines development through project-internal discussion and dissemination of experience so far
- Consider early flagging of ongoing industry initiatives in order to facilitate early identification of topics and optimal engagement time point
- Development through a focus group an aide memoire that can support the submission of proposals for qualification of digital technologies

The evolving framework for innovation: Next Generation Sequencing (NGS)

Industry presented on the regulatory challenges associated with Next Generation Sequencing (NGS) covering setting of performance goals, lack of standardisation, transparency in labelling, rapidly evolving hardware/software as well as evidence requirements for the investigational setting. EMA highlighted that the future regulation of NGS as Companion Diagnostics (CDx) has been considered in the 2017 published concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle. Further considerations have been subject to the multi-stakeholder workshop organised Q2 2017 and will be taken into account during the drafting of the guideline. It was also noted that some aspects mentioned by industry are reflected in CHMP and ICH guidance. Generally, the usage, relevance and integration of NGS technologies in health care decisions are expected to increase. EMA is looking forward to continue a multi-stakeholder approach for the implementation of the IVD Regulation including the regulation of NGS technologies used as CDx.

FOLLOW-UP:

- Invitation for further exchange on the types and numbers of NGS and other technologies that are expected to emerge, to prepare for project-specific engagement as required

Current challenges in developments with biomarkers

Patient selection biomarkers are identified and selected to aid in the identification of patients most likely to respond to a given therapeutic with acceptable side effects. Due to the improved understanding of disease biology, it is increasingly common that new therapeutics are supported by a

companion diagnostic, both during their development and later, in clinical application. It is noted though that companion diagnostics are often developed by a single sponsor as part of a specific development plan. Resulting challenges include that a number of different companion diagnostics can exist for same intended use; potential for subjectivity in the way the tests are utilised; different reagents may be used in each test; some "locally-derived" tests may be utilised in development and post approval; and different assay cut-off values. The importance of collaboration in this space was exemplified using the Blueprint initiative and the TMB harmonisation project. Such efforts for harmonisation were noted as being very important to address the challenges. Furthermore, more information on biomarker development and related data need to be made available to inform decision-making at every stage. Opportunities for such increased communication were identified.

FOLLOW-UP:

- In the context of product-specific development and evaluation activities, need to provide relevant data (eg in the submission dossier) and present them as appropriate (eg labelling), also to provide information to down-stream decision makers
- Seek opportunities to engage on the validation of biomarkers early in drug development
- Need to maintain awareness of existing and upcoming initiatives and use of their outputs

Reflection on perspectives for scientific advice

Industry provided reflections on better use of scientific advice as a continuum along the development life-cycle, pointing out that while the current framework offers many tools and touch points, these can be isolated engagements with separate parts of the EU regulatory ecosystem. For example, advice and feedback from different parts of the system can sometimes be disconnected e.g. from SAWP or PDCO vs. NCA Clinical Trial Units and across similar studies. There is also a need to meet fast-paced development timeframes. Industry supports that a focus group on exploring opportunities leading to a more integrated R&D support could be undertaken.

EUnetHTA presented the experience with parallel consultations from the EUnetHTA perspective explaining the rationale behind allocating consolidated versus individual procedures and quantifying their relative proportion, the therapeutic areas, and SME/ATMP/Orphan breakdown. In terms of experience by sponsors, EMA presented the preliminary results and initial reflections from a feedback questionnaire on Parallel Consultations that took place between August 2017 and August 2018.

The response rate to the first batch of questionnaires was 68% (15 out of 22). Feedback on communications, logistics, HTA participations rates, PCC/PCI allocation rates, alignment between HTA and EMA and intended implementation were highlighted. It was confirmed that PC facilitated a single development trial/plan approach, and meeting the evidentiary needs of the involved stakeholders according to 46% of respondants, whereas all respondants indicated that their expectations were met partially or fully, and that they would repeat the process for a different indications. Areas for potential optimisation of the process have been identified through the feedback. Further bilateral discussion between EMA and EUnetHTA will be held to discuss the results.

FOLLOW-UP:

- Initiate the focus group on further development of SA as a continuum spanning across EMA-internal development support activities as well as other partners / decision makers
- In depth review of the survey results on parallel consultation by all participants and subsequent opportunities for interactions to further optimise the process based on this feedback

Opportunities for "Post-licensing evidence generation" (PLEG) proposals in scientific advice

An update was provided from the focus group on PLEG advice, which had the objectives to identify barriers to seeking such advice and identifying solutions. In essence, a major barrier was the lack of information or common understanding of the issues involved, and that there are different approaches to address these. Therefore, the involvement of EUnetHTA was noted to be particularly important in the focus groups to understand HTA needs and approaches in this area. It was also stressed that communication on the issues surrounding the advice on PLEG would serve to address such a principal barrier.

A paper will be the output of the focus group with the aim to serve as a discussion tool for medicines developers and other stakeholders, to encourage and facilitate proactive PLEG scientific advice discussions. The paper is expected to cover the following areas:

- What is PLEG? • What PLEG has been requested previously? • Why seeking advice on PLEG and when is the best time for advice? Considerations for PLEG advice early in development.
- PLEG advice post decision making • How to seek PLEG advice, for which products and which questions to target?

The aim is to finalise the document in Q1 2019, and have it published in a peer-reviewed scientific journal.

In addition, EUnetHTA presented the roles of PLEG for HTA bodies, the EUnetHTA criteria for PLEG, and for Early Dialogue (ED) on PLEG. Differences between early dialogue on PLEG and so called "work package 5b PLEG pilots" by EUnetHTA were discussed as well as the interactions between Work packages 5b and 4, at the stage of PLEG pilots, and the timing of different events. The information was complementary to better understand ways to optimise obtaining advice on PLEG.

FOLLOW-UP:

- Finalisation of the PLEG advice discussion paper with a view to prepare a publication in a scientific journal

Experience with orphan designation reviews

As part of the EMA/EUnetHTA work plan activities, a joint study is being conducted with the aim to assess similarities and the differences between the SB assessment within the orphan framework assessment process as practiced by the EMA (COMP) and the REA as part of the HTA of orphan drugs as practiced by HTA institutions across Europe. This is a qualitative, retrospective, descriptive and comparative analysis of secondary data from five case studies and so far the initial analysis has been completed. It could be seen in these cases that SB assessment and REA frameworks share similar aspects, for 50% of cases no differences were demonstrated; most differences were found on the comparators considered. The detailed analysis of the five exemplary drugs is ongoing.

A second topic on orphan medicines concerned the experience with similarity assessment. The need for such assessment can apply to any product whenever there is an orphan product authorised already for a condition related to the proposed therapeutic indication. Elements to be considered are molecular features, mechanism of action and the therapeutic indication. The revision of Orphan Regulation (EC) No 847/2000 was noted. To stimulate a wider reflection on the topic, practical experience with such similarity assessments was invited.

FOLLOW-UP:

- Finalisation and publication of the EMA/EUnetHTA analysis on the comparison between significant benefit and relative effectiveness assessment
- Invitation to provide feedback on industry experience with the similarity assessments, for more detailed discussion at the next platform

Topics from the paediatric action plan

Several topics related to the published EMA/EC action plan on paediatrics were discussed. In terms of facilitating cross-committee interactions, an overview of the experience with the recently established CHMP/PDCO joint session during the committee plenaries was presented. This covered the objectives, the format and the outcome of the interaction. Furthermore, feedback from a survey amongst participants was summarised, highlighting the value that is seen in such engagement.

Another topic concerned the reflection on alternative PIP models. Given the requirement to submit a PIP early in development and keeping in mind the course of pharmaceutical development, a more 'evolutionary' approach to agreeing PIPs may be considered. The aim would be to optimise the reflection of knowledge gain over time. Different options for optimising the PIP procedure and enabling resource-efficient adjustments to evidence generation were discussed.

Industry suggested early involvement of the Scientific Advice Working Party in order to receive regulatory feedback without engaging in a binding, detailed PIP opinion at that time. EMA and PDCO representatives stressed the importance of early involvement of the PDCO. Various ideas for enabling the provision of PDCO feedback early, prior to a binding PIP opinion were discussed. However, it was mentioned that binding PIP elements early on might be necessary to push for tackling scientific challenges, resources, and overall for timely paediatric development. Potentially elements of different models may be combined with flexible interaction opportunities along the way of paediatric development.

FOLLOW-UP:

- Further exchanges on the various elements for a PIP model that adjusts to evidence generation and opportunities for revisions in the PIP guideline, in the context of the action plan

Parallel break-out sessions

In the margins of the platform meeting, two break-out sessions took place:

- Histology-independent development in oncology: high-level exchange on the current challenges and discussion on future engagement opportunities
- Options for a PIP model that adjusts to evidence generation: exchange on ideas for a PIP model that allows, in certain cases, to develop along with the evolution of scientific knowledge

The objective was to allow for an exchange of views on more conceptual topics; furthermore the discussion allowed for identifying future activities and opportunities for interaction.