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Highlight report of the 6th Industry stakeholder platform on research and development support

4 June 2021

Role	Name
Chair:	Michael Berntgen
Present:	Industry: **AESGP** Birgit Ewert, Klavdija Kmetic, Mike Picchioni **Alliance for Regenerative Medicine** Francesca Buttigieg, Marcello Milano, Mark Friedman, Michael Werner, Oluwayemisi Corinaldi, Valerie Salentey **EFPIA** Amanda Matthews, Christine Mayer-Nicolai, Emma Du Four, Genevieve Le Visage, Isabelle Stöckert, Jacquelyn Awigena-Cook, Sini Eskola **EUCOPE** Andrea Braun-Scherhag, Jill Morell, Joao Duarte, Lars Hyveled-Nielsen, Laura Lieber, Lucia D'Apote, Maren von Fritschen **EuropaBio** Bettina Doepner, Christiane Abouzeid, Esteban Herrero-Martinez, Ian Hawkins Kara Daly, Susan Bhatti, Violeta Georgieva **Europharm SMC** Sónia Ferreira **Medicines for Europe** Anabela Godinho, Beata Stepniewska, Keith Watson, Marta Baldrighi, Paul Scannell, Susana Almeida, **Vaccines Europe** Anna Czwarno, Karen Jourdan–Brown, Muriel Paste, Serge Mathonet, Solange Corriol Rohou, Susanne Heiland-Kunath. EMA: Alexis Nolte, Ana Hidalgo-Simon, Camille Vleminckx, Caroline Pothet, Christelle Bouygues, Falk Ehmann, Francesco Pignatti, Iordanis Gravanis, Jordi Llinares Garcia, Kristina Larsson, Marie-Helene Pinheiro, Michael Berntgen, Nathalie Bere, Paolo Tomasi, Pascal Venneugues, Radhouane Cherif, Ralph Bax, Sonia Ribeiro, Xavier Kurz, Zaide Frias. EMA scientific committees and working parties: Anja Schiel, Violeta Stoyanova-Beninska. European Commission: Chloe Spathari, Fabio Datri, Flora Giorgio, Hanim Yassin, Kaia Kantorska, Rocío Salvador Roldán, Sara Rafael Almeida. Other: **Medtech Europe** Merlin Rietschel, Oliver Bisazza, Petra Zoellner **Medtech & Pharma Platform Association** Shayesteh Fürst-Ladani, Stephan Affolter.

This was the sixth occasion in a series of regular meetings between regulators and representatives of industry stakeholder organisations to address 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.

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As part of the introduction a review took place of the status of follow-up actions from the last platform meeting. Significant progress has been made on these items, and several are subject to follow-up discussions at the 6th meeting. Of those not in scope of the agenda, the following developments were highlighted:

- Regarding the pilot of tailored scientific advice for biosimilar developments it was confirmed that the analysis has been completed and discussed with the working parties and committees. As reported last time, the pilot was successfully completed with the pre-specified number of scientific advice procedures. Both developers and regulators who took part in the pilot were generally positive about the experience. They attributed value through the opportunity for more in-depth discussions and resulting guidance. It was concluded that such tailored scientific advice framework for biosimilar development will be implemented as part of regular scientific advice operations, with certain adaptations to the process. The EMA website will be updated and the report from the pilot published.
- In terms of items raised in the context of the implementation of IRIS for scientific advice, the role of IRIS Industry Coordinator (aka "general manager") is being tested and should be released in production shortly, guidance on research product identifiers (RPIs) requests and transfers has been updated, and bug fixes have been implemented by the technical team. Looking at engagement on future developments for IRIS, two collaboration teams with Industry for Marketing status and Inspections have been set up.

Combination products with Medical Devices / Companion diagnostics

A. Practical arrangements regarding (integrated) drug-device combination products under the Medical Device Regulation

EMA provided an update on the status of the update of the Q&A on the implementation of the MDR and the guideline on quality documentation for medicinal products when used with a medical device. The Q&A update aims to provide key clarifications on requirements for integral, co-packaged and ancillary medicinal substances in medical devices. This includes clarifications on existing questions and the addition of seven new questions. Furthermore, an update of application forms for Initial Marketing Authorisation and Variation applications is in progress. The scope is to have more granularity on the device presentation type i.e. integral, co-packed, referenced in PI (medical device or companion diagnostic) and information on documentation (declaration of conformity, CE certificate or NB opinion) provided in the application.

Regarding the Guideline on quality documentation for medicinal products when used in combination with a medical device, the scope is on product-specific aspects of a medical device relevant to the quality, safety and efficacy of a medicine. Whilst the discussions are still ongoing, it was confirmed that the guideline has not fundamentally changed after public consultation. Particular points of interest were minimising the duplication of review by EMA/NCAs vs Notified Bodies, replacement of the platform concept with use of supportive data, and removal of the proposal for Notified Body Opinion template. Looking at the publication of these documents, for the Q&A update the target is in June, with the final quality guideline as soon as possible after Q&A publication.

Industry representatives welcomed the developments, particularly the workshop EMA had organised in November 2020, stressing the urgency. It was noted that implementation of Article 117 of the MDR requires a strong collaborative approach across industry, regulators and notified bodies; also additional guidance is needed by industry for drug-device combination products. The update on the above-mentioned Q&A as well as the guideline on the quality requirements for drug-device combinations were

noted. Other points raised by industry were lifecycle management and substantial changes as well as utilization of a 'platform' approach and the NB opinion. In the discussion the importance of these items was noted and subsequent follow-up activities were agreed.

FOLLOW-UP:

- EMA, in consultation with the EC, to finalise and publish the update of the Q&A (2.0) to provide clarifications on requirements for integral, co-packaged and ancillary medicinal substances in medical devices
  (post-meeting note: for published document see Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (europa.eu))
- EMA to the update application forms for MAA and variations in collaboration with the CMDh and EC.
- EMA to finalise and publish the guideline on quality documentation for medicinal products when used with a medical device, subject to EC consultation feedback.
  (post-meeting note: for published document see QWP-BWP Guideline on medicinal products used with a medical device (europa.eu))
- EMA will consider the need to develop further guidance on life-cycle management and devices changes, based on the experience gained and, as needed, involve industry stakeholders.
- EMA to consider further dialogue on specific aspects (e.g. framework for 'platform approach' with stakeholders in the context of the Regulatory Science Strategy to 2025 implementation and development of an 'integrated pathway' for complex drug device combinations)

B. Preparation for Companion Diagnostics review under the In vitro Diagnostics Regulation

EMA provided an update on the implementation of the consultation procedure on Companion Diagnostic (CDx). The steps taken to collaborate with Notified Bodies (NBs) started in 2019 and led to the setup of the CDx consultation Working Group in March 2021. This group is composed of EMA/CHMP/CAT experts, NB subgroup, the European Commissions and NCAs responsible for medical devices. This group provides an opportunity to have two-way dialogue on data requirements for IVD (CDx) conformity assessment and NB review and scope of CHMP scientific opinion on CDx suitability with medicinal products. It also supports the development of EMA/CHMP/CAT procedural guidance on the consultation of CHMP by NB on CDx, and aims to prepare for first applications on legacy IVD-CDx (pilot of real cases). The procedural steps for CDx consultation are currently under discussion. The timepoints cover different scenario regarding development of CDx for a new predictive biomarker for personalised medicinal product; also data package and scope for the CDx consultation are being reviewed. The expected outputs are a draft procedure for consultation between NB and EMA/NCA, a draft CHMP opinion template together with guidance to assessors, and piloting of cases.

Industry stressed the complexity of co-development pathway and the need for integrated development & review pathways. Several issues and proposals were put forward. Also the readiness of the system in view of the implementation of the IVDR was highlighted. The European Commission took note of these issues.

FOLLOW-UP:

- EMA, in collaboration with NBs, to develop the consultation procedure between Notified Bodies and EMA/NCA on companion diagnostics and consider opportunities for industry consultation and Industry involvement for piloting of real cases.

- EMA to consider what level of information on assay/CDx will be needed in the labelling of medicinal product

Assessment of Similarity for Advanced Therapy Medicinal Products

EMA provided an overview of the updated Q&A document related to the assessment of similarity for ATMPs in the context of the orphan legislation[1] released by the European Commission in April 2021. This document provides practical guidance to developers of ATMPs on the application of the concept of "similar active substance" within the meaning of Commission Regulation (EC) No 847/2000 as amended by Regulation (EC) 2018/781. This update was led by the European Commission with input from several CAT members to reflect recent experience (including from scientific advice and initial marketing authorisation applications) and new developments in this field. Specifically, concrete examples of situations that could support a claim of non-similarity (when associated with a significant impact on the biological characteristics and/or activity of the product) were shared, and guidance on the level of evidence expected to support non-similarity claims was discussed. The Agency also highlighted the ongoing development of a guidance on the structure and properties for the determination of new active substance (NAS) status of biological substances to which CAT is contributing and will address ATMPs.

Industry representatives provided positive feedback on the updated Q&A but called for more meaningful pre-submission discussions on similarity, including around the interpretation of significant impact and required level of evidence. On this point, Industry was encouraged to raise such discussion in relation to concrete cases during pre-submission interactions and/or scientific advice. Industry also raised their interest for future targeted forums similar to CAT interested parties' meetings to discuss areas specific to ATMPs, such as the inter-relationship between non-similarity and NAS claims.

FOLLOW-UP:

- EMA to consider a follow-up on proposed areas of interest in specialised forums, following consultation with the CAT.

Progressing the concept of patient-centred development in practice

The Agency updated on proposed ICH guidelines for a harmonized approach to inclusion of the patient's perspective in medicines development and regulatory decision making. Two guidelines are proposed: use of patient-reported outcomes (PROs) and other clinical outcome assessments (COAs), and trade-offs between benefits and harms. The public consultation concluded March 2021 and input will be considered for next steps (update RP, guideline work).

EMA also advised on upcoming mapping work with academics to support development of guidance on collection and use of patient (experience) data for regulatory purposes. The research will analyse methodologies, definitions, experience, use and new methods (digital technologies), and will provide recommendations on robust/relevant/feasible methods. Finally, an overview was given on patient involvement in COVID activities at EMA and the development of an overarching engagement strategy.

Industry representatives presented their thoughts on next steps regarding generation and inclusion of patient evidence in regulatory submissions, reporting by patient community and guidance development. They surmised how can stakeholders utilise the same patient data to minimise duplication and enable patient/multi-stakeholder discussions? A proposal was made to establish a multi-stakeholder group with industry, patients and regulators.

[1] https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/2018_qa_atmps_en.pdf

Furthermore, industry provided an update on IMI PREFER; a framework and recommendations for preference exploration and elicitation methods for use in patient preference (PP) studies. PREFER outcomes should be considered in upcoming guidance. Representatives also enquired how patient evidence should be included in submissions and later communicated, e.g. labelling, EPAR.

The "science of patient input" refers to systematic collection and incorporation of methodologically-sound patient data throughout the drug development lifecycle. To achieve this, fit-for-purpose methods and tools should be developed and implemented. It was proposed to consider establishing an EMA-sponsor dialogue platform dedicated to discussing collection and use of patient input.

FOLLOW-UP:

- EMA to consider hosting a multi-stakeholder meeting on 'patient engagement' and 'patient data generation' late 2021 / early 2022, (subject to business continuity / COVID-19 related priorities)

Scientific advice for continuous innovation in known molecules

Industry outlined needs from developers' perspective concerning scientific advice for continuous innovation in known molecules, starting from the proposition that the process for innovating known molecules, known as continuous innovation, differs from traditional R&D approaches. Proposals included to allow "spin-off" and iterative advice, branching off the main SA request; align SA with payers and notified bodies data requests, along a common thread; expand SA provision to better cover use of RWD/RWE; provide the option of receiving integrated regulatory advice in SA processes; ensure that EMA SA is taken into account by NRAs in DCP dossiers. Several proposals were made to address these needs. During the discussion, it was stressed that the scientific advice framework is sufficiently flexible to cater for specific needs of a programme. The need for iterative advice and the engagement with other decision makers was also raised in the ongoing Focus group discussions (see below). Therefore, companies aiming for such development of a known molecule are invited to discuss directly with EMA's Scientific Advice office how to best manage a specific request.

FOLLOW-UP:

- Industry invited to provide concrete cases of developments programmes to define in a pre-submission phase the specific needs for the scientific advice request

5-year review of the PRIME scheme

The Agency provided an update on the surveys on PRIME, intended to collect feedback on developers experience with the support received for PRIME products, to inform the review of the performance of the PRIME scheme. The EMA product specific surveys would be complemented by a general survey run by trade associations to gather broader Industry's views on the PRIME scheme at company level. The surveys would run between 7 June and 30 June; Industry was encouraged to make use of this unique opportunity to provide feedback on experience with PRIME after 5 years of launch of the scheme. The analysis of the results would be discussed at the next platform meeting in 2H21.

FOLLOW-UP:

- EMA and trade associations to launch the respective surveys independently, for industry to provide feedback
- Follow-up discussion at the R&D platform in 2H21

Status update from the ongoing discussions at the recently established Focus Groups

Practical application of integrated development support

A short update of the Focus Group work to date was presented. This included a presentation of the previously agreed design principles (please refer to see the highlight report of the 5th Industry stakeholder platform on research and development support) to be applied to the analysis of PRIME and COVID-19 developments (although not exclusively) serving as case examples towards further evolution of the scientific advice framework. Moreover, the Focus Group has agreed on the format of case information collection and the rules of such information sharing to ensure confidentiality of proprietary information while allowing a sufficient level of detail. Next steps include case collection and analysis towards formation of concrete proposals changes to the scientific advice framework. In this context the current regulatory capacity challenges due to high numbers of scientific advice requests were noted.

Concept of an 'evolutionary' PIP

The objective of this Focus Group is to explore a PIP model that allows, in certain cases, the paediatric development programme to become more defined over time as more evidence becomes available. The group should discuss possibilities for and limitations of such PIP model that allows to develop along with the evolution of scientific knowledge. An overview of the criteria established by the group so far was provided. In terms of concepts, two options are being explored: 1/ "Two-step PIP2 with the filing of a "proof-of-concept PIP" with high level description upon completion of adult PK studies, followed later by PIP with more detailed measures based on generated data; 2/ Better use the concept of 'duly justified' for the timing of PIP application, with discussion within SA or integrated dialogue, followed by PIP filing with detailed measures once this is possible based on generated data and advice input received. Further details, operational aspects, inherent risks and benefits are being discussed by the group in upcoming meetings. The outcome and proposal(s) will be presented at 7th R&D platform.

FOLLOW-UP:

- Report on the outcomes of the focus groups on "Practical application of integrated development support" and "Concept of an 'evolutionary' PIP" at the R&D platform in 2H21

Headline results from a study on submission of Real-World Evidence in Marketing Authorisation and Extensions of Indications applications

EMA provided data from a study characterising RWD/RWE included in centralised marketing authorisation applications (MAA) and extensions of indications (EoI) submitted in 2018-2019 and exploring its contribution to benefit-risk decision-making. The preliminary results showed that RWD/RWE is used in 40% of MAAs (mainly post-authorisation) and in 18% of EoIs (mainly pre- or post-authorisation). The majority of products are in the areas antineoplastic and immunosuppressants (35% MAA and 42% EoI). When used pre-authorisation they come mainly from studies looking at efficacy/effectiveness; when used post-authorisation they are mainly RMP Category 3 (for studies included in RMP) looking at safety. A scientific publication is in preparation.

FOLLOW-UP:

- EMA to finalise the study analysis for more detailed discussions with developers, e.g. at the EMA / HMA workshop on the Big data learning initiative for application of RWE