20 January 2021
EMA/619777/2020

Highlight report of the 5th Industry stakeholder platform on research and development support

16 November 2020

Role	Name
Chair:	Michael Berntgen
Present:	Industry: **AESGP:** Klavdija Kmetic, Mike Picchioni, Stephanie Pick **Alliance for Regenerative Medicine:** Angela Johnson, Anne-Virginie Eggimann, Patrick Ginty, Stéphane Denepoux, Tara Elvang, Vinciane Pirard **EFPIA:** Alan Morrison, Emma Du Four, Genevieve Le Visage, Gesine Bejeuhr, Isabelle Stoeckert, Mats Ericson, Nadege Le Roux, Sini Eskola, Susan Longman **EUCOPE:** Andrea Braun-Scherhag, Angelika Joos, Cécile Ollivier, James Witty, Joao Duarte, Lars Hyveled-Nielsen, Lucia D'Aporte, Maren von Fritschen **EuropaBio:** Aimad Torqui, Bettina Doepner, Christine Mayer-Nicolai, Esteban Herrero-Martinez, Jill Morrell, Violeta Georgieva **Europharm SMC:** Francesco Florio, Jozseph Pallos **Medicines for Europe:** Beata Stepniewska, Julie Marechal-Jamil, Marta Baldrigni, Sabrina Conti, Susana Almeida **Vaccines Europe:** Claire Hill-Vennig, Inge LeFevre, Laurence Allard, Monica Pagni, Muriel Paste, Virginia Acha. EMA: Michael Berntgen, Alexis Nolte, Antonella Baron, Armin Ritzhaupt, Corinne de Vries, Efthymios Manolis, Francesca Cerreta, Francesco Pignatti, Gunter Egger, Iordanis Gravanis, Juan Garcia, Klara Tiitso, Kristina Larsson, Marie-Helene Pinheiro, Nathalie Bere, Paolo Tomasi, Radhouane Cherif, Ralf Herold, Ralph Bax, Sonia Ribeiro, Spiros Vamvakas, Tarita Toufexi, Veronika Jekerle. EMA scientific committees and working parties: Harald Enzmann, Sabine Scherer, Anja Schiel, Violeta Stoyanova-Beninska. Other: Dario Pirovano (Medtech Europe), Fabio D'Atri (EC), Kaja Kantorska (EC), Merlin Rietschel (Medtech Europe), Tidde Goldhoorn (EC).

This was the fifth 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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Experience with the R&D stakeholder platform

The experience so far with the industry stakeholder platform on research and development support was reviewed. Since its inception, four meetings of the platform were held (1st R&D platform meeting - 25.04.2017, 2nd R&D platform meeting - 15.11.2017, 3rd R&D platform meeting - 18.05.2018, 4th R&D platform meeting - 23.11.2018); industry stakeholder platforms were paused in 2019 due to business continuity considerations. To maintain a constructive working environment, the number of participants is limited and the selection based on the items for discussion; committee representatives as well as the European Commission are invited and additional attendees (e.g. HTA bodies) did attend. In terms of topics, the scope is either related to regulatory review processes (around 30% each concerning scientific advice, orphan designation or paediatric development, and 10% on PRIME) or more general on evidence generation approaches (e.g. real-world evidence, digital technologies). Follow-up actions were publication of guidance or other outputs, calls for evidence generation proposals, follow-up discussion (e.g. in focus groups), additional information gathering / analyses, as well as technical operational implementation. Three Focus groups with concrete outputs were held: Post-licensing/launch evidence generation; Qualification of digital technologies; Integrated R&D product support. Overall, the R&D stakeholder platform was recognised as collaborative forum for progressing relevant topics in terms of development support from regulatory perspective, and beyond, as well as evidence generation concepts. Achievements from the R&D platform can contribute to the implementation of strategies such as the RSS to 2025 as well as the EMAN strategy.

Evolution of the scientific advice framework

Discussions on scientific advice revolved around the outcome of the Focus group on integrated R&D product support created in follow-up to the previous platform meeting on R&D support, reflections on iterative and more integrated advice, taking stock of the experience with COVID-19 and the preliminary results of the analysis of tailored biosimilar scientific advice pilot.

The Focus group on integrated R&D product support concluded its activities with the agreement of principles which should direct the further evolution of the scientific advice framework. These include:

- an ecosystem integrating different advice opportunities and ensures engagement across stakeholders;
- flexible advice mechanisms balancing timeliness with complexity;
- good institutional memory of all advice;
- an agile system to extract learnings from scientific advice and make them publicly available;
- availability of best multi-stakeholder expertise for cutting edge technologies and complex healthcare solutions;
- connection between regulators, academia, patients, clinicians and developers;
- stewardship to provide guidance through the different advice / interaction opportunities;
- appropriate funding of resources for high quality interactions.

A practical example of iterative scientific advice in the case of PRIME-designated products was presented by EMA. Such iterative advice is facilitated by the early nomination of relevant EMA product team members and allows repeated interactions and regulatory support during development. The EMA further shared the experience with rapid scientific advice procedures for medicines proposed for the prevention or treatment of COVID-19. 50 rapid scientific procedures were completed by the time of the

meeting, generally within the intended timeframe of 20 days which implies a halving of the shortest regular scientific advice timelines. The process is efficient and maintains high quality of outputs, as working parties' and committees' input is adapted to the shorter timeline and relevant experts participate regularly in frequent teleconferences of the COVID-19 EMA Task Force. On the other hand, this poses challenges with regards to assessment resources and workload. EMA stressed the importance of early and transparent interaction by industry towards a fruitful conduct of rapid scientific advice procedures.

Industry representatives acknowledged the value of the agility of the rapid scientific advice process and particularly the short and pragmatic validation and review timelines and the existence of dedicated contact points which additionally allowed ad hoc consultation and provision of regulatory guidance. Similar experiences were reported in relation to other regulatory activities, e.g. discussions on paediatric investigation plans, variations for GMO derogations and rolling reviews. At the same time, additional challenges were highlighted stemming from scientific and technological advances enabling the development of increasingly complex medical interventions or leading to innovative pharmaceutical quality or manufacturing changes.

The regulatory adaptations for COVID-19 were considered essential elements of the evolutions proposed by industry for scientific advice towards diversifying and integrating the provision of regulatory advice along the development continuum, in line with the EMA Regulatory Science Strategy to 2025. These evolutions should include:

- Orientation and stewardship through the different regulatory interaction possibilities (e.g. scientific advice, paediatric investigation plan, Innovation Task Force etc.) and EMA committees and working parties (PDCO, COMP, CAT, SAWP, QWP, PRAC, CHMP, IWP);
- Iterative interactions allowing integration of input from specialised experts for complex products, various essential stakeholders (CTFG, Notified Bodies, NITAGs, HTA organisations/payers) and regulators from different jurisdictions;
- Technical support which helps maintain institutional memory of interaction and allows easy engagement of relevant committees/stakeholders/experts, while safeguarding the confidentiality of information.

The experience from the completed pilot on tailored biosimilar scientific advice was presented, focusing on the actions taken to analyse the experience and on the preliminary learnings. In the pilot, developers had been invited to present as extensive as possible analytical and biological data packages to better adjust the extend of in vivo animal and clinical study requirements. Preliminary learnings showed that developers considered the requirements for advanced Quality data packages as a hurdle to enter the pilot, while regulators concluded that the extent of the advice provided had been limited by the fact that the data packages presented were fairly immature. Ultimately, the concept of the stepwise biosimilar development appears often applied differently in practice, as generation of quality comparability data takes place in parallel with clinical development. Nevertheless, industry representatives expressed their appreciation for the pilot and recommended to implement the provision of this type of scientific advice as an option for biosimilars.

FOLLOW-UP:

- Follow-up discussion in a Focus group on testing the design principles through practical cases for integrated development support, in the context of COVID-19 developments or PRIME developments. This group should also identify opportunities for targeted modifications in existing processes, should they lead to potential for efficiency gains.

- Publication of the EMA report on the experience with the pilot of tailored scientific advice for biosimilar developments, including recommendation for future arrangements.

Launch of IRIS for scientific advice

Industry noted positively the agility and speed of development of IRIS for Scientific Advice, and the responsiveness of the EMA Servicedesk. Robust User Acceptance testing was identified as a key factor to help industry to prepare for the rollout of future expansion of the system. Proposals from industry included: written process for RPI and their maintenance; more granularity for access management (roles and deputies); dashboard of past and ongoing company activity; automated download and upload of data in Excel/CSV files; list of all IRIS source/integrated data beyond SPOR; publications on the EMA website in addition to IRIS Forums; possibility for further engagement (e.g. multi-stakeholder IRIS platform, group of "super-users").

EMA presented the outcome of the first Scientific Advice submissions. The main two feedback considerations provided to industry were:

- Clarification on the difference between substances (managed in SMS/EUTCT, not linked to a specific organization, and requested via EMA Servicedesk) and Research Products (Research Product Identifier [RPI] to be requested via IRIS, after the substance[s] is/are added to SMS/EUTCT as current and "authorised").
- Advice to Industry on the need to reconcile the assignment of all regulatory entitlements (e.g. orphan designations) and RPIs to the same OMS location of a parent organisation, normally the location which is the legal seat of the organisation.

FOLLOW-UP:

- Follow-up on items raised in the context of the implementation of IRIS for scientific advice as well as engagement on future developments for IRIS together with the relevant operational functions, in the appropriate communication channels.

Follow-up on the practical arrangements regarding integrated drug-device combination products

The joint industry presentation reflected on the significant, constructive, efforts that were made by all stakeholders since the last R&D stakeholder forum and welcomed the opportunity of the planned webinar on the implementation of MDR Article 117 to discuss specific case examples and the time allocated for broader discussions. Equally, industry representatives stressed that finalisation of the quality guidance on drug-device combinations is urgently needed to provide certainty for when Art 117 becomes fully effective. With the increased use of medical devices in combination with medicinal products, reference was made to the increased use of software in drug-device combinations and that an integrated pathway as proposed in the EU medicines network strategy would allow EMA to bring together a network of European expertise to be used in support of development (e.g. scientific advice), marketing authorisation and life-cycle management.

EMA reiterated that the implementation of the new devices legislation where there is an interface to medicinal products is a complex process but that significant progress has been achieved as a result of the collaborative effort of all stakeholders. The EU medicines network strategy will be an opportunity to build stronger alliances with experts from medical device authorities and others to prepare for the next generation of complex healthcare products.

FOLLOW-UP:

- Publication of the final guidance on quality requirements for combination products as well as the Q&A on the MDR/IVDR implementation.
- Detailed discussion on Article 117 implementation at the workshop on 27.11.2020.

Enhancement of the PRIME scheme

EMA presented first reflections on the enhancement of the PRIME scheme. PRIME aims to provide enhanced support to transformative products during their development. The concept goes beyond a "label", a series of Scientific Advices, and later Accelerated Assessment. The PRIME scheme is both a regulatory and a scientific support tool, acknowledging that evidence generation is a continuum. A 5-year review of the procedural and scientific elements of PRIME is currently in preparation. Possible analysis parameter should address a clarification of the entry criteria and will include objective criteria to measure a variety of aspects, such as trends of PRIME accepted/rejected and MA outcomes, Follow-up on kick-off plan / integrated development support, as well as acceleration of access for patients (incl. down-stream decision making).

From industry perspective the value of PRIME within the European regulatory system was reaffirmed. Feedback from industry raised positively the value of a key central person to coordinate, connect and give good regulatory support; the pre-submission TC meeting, the benefit of the early Rapporteur appointments, the continuous support to build a continuum knowledge in preparation of the marketing authorisation application, and generally that PRIME acts as a booster to global team and global development approach. Opportunities for enhancement include more opportunities for engagement, including scientific discussions, stronger connection with other processes (e.g. clinical trial authorisation) as well as need for operational flexibility. It was generally noted that such integrated expedited pathway is not a one off but a continuum of interactions.

FOLLOW-UP:

- Conduct of the PRIME 5-year analysis and engage with sponsors in this context.
- Once the analysis is available, further discussion on the procedural and scientific recommendations for enhancement of the scheme, with a view of optimising the scientific interactions, strengthening continuity and streamlining the process.

Progress with the Paediatric action plan

EMA reported that a number of actions in the EMA/EC paediatric action plan had been completed or progressed through a multi-stakeholder effort, despite the fact that work on the action plan had been guided by business continuity considerations. Achievements such as workshops on paediatric medical needs, improvements to global cooperation of decision makers, the publication of recommendations on paediatric clinical trial preparedness, as well as improvements to the administrative and procedural requirements of paediatric investigation plans (PIPs) were highlighted, amongst others. Participants were informed that an interim progress report on the action plan would be published on the EMA website before the end of the year.

Industry representatives presented proposals to optimise regulatory interactions and to improve PIPs and the PIP procedure as well as the PIP compliance check procedure. It became apparent that the PIP process and the implementation of a PIP model, that allows for changes to be made to the PIP in

accordance with evidence becoming available over time, would warrant some further focussed discussion.

FOLLOW-UP:

- Publication of the progress report on the EMA/EC Paediatric Action Plan.
- Establishment of a Focus group to review the proposal for a 'modular PIP' (e.g. definition of cases where this would be needed; procedural step proposal).
- EMA to review industry proposals regarding the handling of the paediatric compliance check.

Progressing the concept of patient-centred development in practice

a) Including patient preferences and patient-reported outcomes in global development programmes, submissions and labels

The industry representatives highlighted the benefits of engaging with patients in drug development and gave an overview of the various ongoing initiatives in this area. They provided some proposals in relation to the use of PROs, and their needs from EMA. This was followed by an overview of how patient preference (PP) data can support benefit-risk decision making, with examples from ongoing IMI project PREFER.

It was discussed that more clarity and guidance is needed on which methodologies to incorporate patient (experience) data that would be acceptable by regulators in benefit risk decision making and also for inclusion in the labelling.

EMA presented preference elicitation methods, with an example of a preference study between EMA, academics and patient organisations. The use of PROs in cancer marketing applications was also presented as an area where more experience exists, and finally some potential guiding principles for assessment and labelling.

b) Industry perspective on optimising interactions between patients, EMA, developers and other stakeholders

The industry representatives gave proposals how interactions between patients, EMA, developers and other stakeholders could be optimised, outlined their needs from EMA with some suggestions how to move forward in this regard, one key being the establishment of a multi-stakeholder group to begin discussions, particularly with regard to implementation of the RSS 2025 recommendations.

EMA gave a general overview of its engagement with patients along the medicine's regulatory lifecycle, especially within benefit/risk discussions, including some key aspects to successful engagement gathered through experience. This was finalised with some highlights on future plans, such as the revision of EMAs framework of interaction, enhancing methods for the generation and use of patient experience data for consideration during regulatory assessments. The need to provide guidance and to exchange methodologies across decision makers was also mentioned.

The discussion following the presentations included an overall agreement on the need to establish a framework which facilitates, guides and supports the generation, use and submission of patient experience data in support of MAA, ideas were shared on how to catalyse progress, leverage current experience and support global alignment (e.g. IMI projects, ICH).

It was felt that a multi-stakeholder discussion could be a good way to continue discussions on this topic in an efficient/sustainable way.

FOLLOW-UP:

- Explore the possibility to establish a multi-stakeholder group to follow-up on the progress with this topic and continue in an efficient/sustainable way (exact scope to be defined, also considering the individual proposals made during the meeting). Implementation and follow-up of this action in the coming months will also deepened on resource availability in view of COVID-19 related activities.