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

25 April 2017

Role	Name
Chair:	Michael Berntgen
Present:	Industry: **AESGP:** Claudine Aziz, **EBE:** Anne Lützhoft Aarbogh, Christine Mayer-Nicolai, Claire Hill-Venning, Gesa Pellier, Isabelle Clamou, Sonja Pumplün, **EFPIA:** Agnes Legathe, Angelika Joos, Elise Melon, Emma du Four, Geneviève Le Visage, Pär Tellner, Virginia Acha, **EUCOPE:** Chay Morgan, James Barnes, Jens Peters, Lars Hyveled-Nielsen, Maren von Fritschen, Martine Zimmerman, Nadège Leroux, **EuropaBio:** David King, Keith Watson, Sarah Highman, Simon Bennet, Vibeke Bjerregaard, Vinciane Pirard, **Medicines for Europe:** Beata Stepniewska, Katja Pecjak, **Vaccines Europe:** Andrea Rappagliosi, Marie-Chantal Uwamwezi, Michel Stoffel, Solange Rohou, Susanne Heiland-Kunath, Victoria Kitcatt EMA: Enrica Alteri, Michael Berntgen, Corinne De Vries, Kristina Larsson, Ralph Bax, Spiros Vamvakas, Marie-Helene Pinheiro, Alison Cave, Armin Ritzhaupt, Chrissi Pallidis, Efthymios Manolis, Falk Ehmann, Francesca Cerreta, Gunter Egger, Irmgard Eichler, Jane Moseley, Laura Liebers, Leonor Enes, Matthias Hofer, Lise Flaunø HTA: François Meyer, Haute Autorité de Santé (HAS)

This was the first 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.

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Evidence generation that addresses different decision makers' needs: the experience with parallel HTA/regulatory scientific advice

In their introductory presentation, industry called for a single European regulatory/HTA scientific advice process building on past experience. This could then also inform future optimised joint European assessment of relative efficacy at market entry. Proposed key improvement for such process should address simplification of logistics, more consistent and predictable HTA engagement, time allocated for discussion and written output from HTA perspective. In addition, it was noted that there is a role for separate regulatory and HTA advice in certain situations.

EMA stated that the existing parallel advice platform is a multi-stakeholder platform developed in agreement with participating HTA bodies. A central component of the platform was that roles and remits of different parties were respected. The platform was open to advice requests also across the lifecycle of the product (very early, pre phase 3, peri-licensing and post licensing) to optimise the generation of evidence for different stakeholders. The numbers of procedures continue to show strong evidence of demand, with the 100th parallel advice procedure now registered. A first parallel qualification procedure had been completed and applicants were encouraged to seek more such procedures. Regarding the output, good agreement has been shown between regulators and HTA in terms of evidence requirements by the completion of parallel advice discussions. Occasional companies have expressed anecdotal concerns that regulators' requirements will be influenced by those of HTA bodies. There is no evidence that this is the case; a joint scientific article published by EMA and participating HTAs [1] showed that for example, even where the parallel advice resulted in agreement between stakeholders, the choice of comparators was firmly rooted in the expected regulatory rationale.

EUnetHTA presented an update on the developments from their perspective; progress is being made on the optimisation of the procedure to enable a single platform for multi-stakeholder parallel advice. EMA has agreed to observe EUnetHTA only early dialogues; EUnetHTA specific named observers are invited to all parallel advice meetings. The latest development by EMA and EUnetHTA are the expected centralised recruitment of HTA bodies for all parallel advice (taking company preferences into account); simultaneous pre-notification of all parallel advices to EMA and EUnetHTA, whereupon, a subset with be selected by EUnetHTA for Early dialogue working party (EDWP) involvement; and enhanced HTA coordination.

FOLLOW-UP:

- Continuous fine-tuning of the existing process, including coordination of engagement and EUnetHTA observership
- Collaborative work of EMA and EUnetHTA – together with the EC - towards a new process addressing the key features
- Review of experience once the new process has been established (e.g. operations, output, coordination)

[1] *Tafuri, G., Pagnini, M., Moseley, J., Massari, M., Petavy, F., Behring, A., Catalan, A., Gajraj, E., Hedberg, N., Obach, M., Osipenko, L., Russo, P., Van De Casteele, M., Zebedin, E. -M., Rasi, G., and Vamvakas, S. (2016) How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. Br J Clin Pharmacol, 82: 965–973. doi: 10.1111/bcp.13023.*

Advances in the co-development process for personalised medicines

This session provided an opportunity to discuss the current thinking on the implementation of the new IVD Regulation with respect to companion diagnostics as a key element for personalised medicine. A number of issues and challenges were highlighted by industry stakeholders, particularly on the future procedural interactions between the different stakeholders during development and marketing authorisation of both companion diagnostic and medicinal product.

EMA identified similar challenges as well as opportunities with respect to the future interaction between the different stakeholders. Experience collected thus far in relation to stratified medicine as well as existing possibilities of engagement with the regulators in form of Scientific Advice was highlighted. Experience gained from the qualification procedure is relevant in shaping the regulatory thinking towards emerging approaches in personalised medicine. The EMA shared an early outlook on procedural aspects of engagement for marketing authorisation applications involving companion diagnostics.

Whilst this interaction was a good start it was recognised that there is need for continuous collaboration and importantly to involve different stakeholders, including notified bodies (NB).

FOLLOW-UP:

- Publication of the concept paper on the co-development of biomarker based companion diagnostics
- Explore potential for using a platform of multi-decision maker scientific advice to cover interactions with Notified Bodies
- Clarification of the interaction during the regulatory assessment for companion diagnostics
- Create opportunities for further, more detailed discussion with all stakeholders and to progress on other topics, e.g. labelling, follow-on CDx, clinical evidence requirements

Learnings and proposals on incorporation and generation of Real World Evidence within development programmes

This session addressed current experience and learnings of both the EMA and industry stakeholders in the use of real world evidence to support the early development phase of drug development. EMA presented what might be the opportunities for real world data and touched on what factors from a regulatory perspective affects the acceptability or not of real world data. The latter part of the presentation highlighted experience and learnings from concrete examples seen during the scientific advice process and the adaptive pathways pilot. Industry stakeholders similarly discussed opportunities for real world data, presented concrete examples and highlighted ongoing challenges around assessing data quality as well as the need to deliver access while ensuring sustainability and appropriate data governance. In particular the need for collaboration amongst all stakeholders was emphasised. In the following discussion the need for engagement with data owners was recognised in order to ensure specific data necessary for regulatory decision making were prospectively collected.

FOLLOW-UP:

- Multi-decision maker SA with HTAs as platform to discuss concrete development proposals
- Explore opportunities for further in-depth discussion, e.g. as part of the Registry initiative, and to develop a more holistic approach

Optimising the guidance on significant benefit demonstration in the context of protocol assistance

EMA presented key observations from 16 years of EU orphan legislation and highlighted the rise of orphan marketing authorisations with significant benefit criterion and the stagnation of requests for protocol assistance with significant benefit input. Hence, EMA outlined the COMP priority to improve early dialogue on significant benefit and invited industry to request PA with COMP significant benefit question more frequently. Industry stakeholders presented their view that it was necessary to ensure that protocol assistance was delivered through a cross committee approach with COMP input on significant benefit in order to ensure predictability of outcomes. In response, EMA explained the PA procedure by the COMP with links to the rest of the EU network and highlighted recent improvements, which warrant quality and predictability of outcomes.

Industry also suggested a more iterative approach to protocol assistance, which would allow for the discussion of critical changes occurring between orphan designation and orphan maintenance. This suggestion was welcomed by EMA. In this context it was clarified that the current fee structure for protocol assistance already promotes iterative protocol assistance.

Finally, industry stakeholders expressed the view that more guidance is needed on the definition of significant benefit including consistency across different legislative provisions and on the demonstration of significant benefit. EMA informed that the need to better understand the different concepts and purposes of “significant benefit” provisions and review how assessment of “significant benefit” is applied across different legislative provisions had already been identified and was included into the CHMP work plan 2017 (1.2.3. Concepts of significant benefit). In addition, EMA announced the intent to publish experience with the demonstration of significant benefit in form of scientific publications.

FOLLOW-UP:

- Publication on the experience with Significant Benefit
- Explore opportunities for additional transparency at time of marketing authorisation with regard to the maintenance assessment

Implementation of the 2016 Notice on the application of the Orphan Regulation

EMA explained the process for re-assessment of significant benefit at time of post-authorisation extensions of indication (falling within same orphan designation). It was clarified that a maintenance report is only needed if the COMP deems that the scope of the extension of indication raises justified and serious doubts on the maintenance of the orphan designation criteria. The COMP will decide if the re-assessment is necessary in a first discussion that can be based on a short justification from the sponsor. If re-assessment is deemed necessary, the process follows the usual procedure by the COMP for maintenance of orphan status at time of marketing authorisation. Industry highlighted potential challenges with the procedure, e.g. in case of a negative opinion from the COMP.

The clarifications in the Notice with regard to what can constitute a significant benefit were discussed. It was noted that EMA is finalising a publication on a review of the experience with the demonstration of significant benefit at time of marketing authorisation. For parallel applications industry welcomed the clarification even though the timing remains challenging. If the time gap between one marketing authorisation to the next is short, relevant and robust documentation to base the indirect comparison

on can be challenging to find. With regard to hospital preparations, industry suggested that they must be available in most member states and need to be recommended in European Clinical guidelines, which is in line with EMA views.

FOLLOW-UP:

- Cascading of information concerning the need for re-assessment at time of extension/ modification of the indication
- Discussion on the experience gain based on the publications due for 2017
- Monitor the impact of the Notice (industry and EMA)

The concept of early dialogue for paediatric development plans

A pilot was launched in June 2015 in order to encourage dialogue on paediatric drug development between the Agency and applicants at very early stages of medicine development. The intended scope of the early dialogue meeting has been to define the appropriate condition and target population for which the product should be developed in children, and to encourage early reflection on the paediatric development strategy and its integration into the overall development plan (e.g. inclusion of adolescents in adult trials, extrapolation).

During the pilot phase applicants may not have made full use of this interaction, as indicated by the low number of requests received. Moreover, only 9 out of 36 (25%) requests for an early interaction meeting were in scope of such a meeting. Most of the received requests related to products whose development was already at advanced stages when a paediatric investigation plan (PIP) submission is required in line with the Paediatric Regulation and/or where detailed methodological questions were asked that would be suited for discussion during a PIP or Scientific Advice procedure. Feedback from industry showed that more clarity may be required regarding the optimal timing of this interaction and how it fits in with other interactions offered by the Agency (e.g. Scientific Advice, PRIME). However, overall the opportunity for such interaction has been appreciated and deemed useful even though the scope and operations should be reconsidered and fine-tuned in order to meet expectations of all parties.

FOLLOW-UP:

- Re-design such platform for early interaction taking into account that paediatrics need to be integrated into overall development programmes

Facilitating engagement with the FDA to allow shaping paediatric development programmes

Industry presented the views on facilitating engagement on paediatric development with the EMA and FDA, stating that global paediatric development is warranted for the benefit of children, to optimise product development, to avoid unnecessary replication of or unnecessary divergence in paediatric studies. It was raised that participation of sponsors in the existing dialogue between the two agencies would be valuable, in particular for programs with identified divergences, along with streamlining available regulatory tools (pipeline meeting, ITF, PRIME, SA) and optimising their use. Four options to facilitate global paediatric development programmes were presented together with an outline of opportunities and potential challenges for each of them: **Option 1**: Parallel EMA/FDA scientific advice including paediatric experts; **Option 2**: Joint pre-submission meeting with scientific discussion;

Option 3: Enhanced common commentary during PIP/PSP process; **Option 4**: Mutual reliance on paediatric plan assessment.

EMA reported on the experience with the EMA-FDA paediatric cluster and presented the most recent statistics, including the increased number of common commentaries, a tool to inform sponsors of the product discussion at the Paediatric Cluster. As a follow-up of an EU-US strategic meeting on the future of paediatric medicine at the EMA in September 2016, several measures have been implemented to allow further streamlining global paediatric product development, such as

- the opportunity members of PDCO and the Paediatric Medicines Office (PME) to call into the weekly Pediatric Review Committee (PeRC) meeting and vice versa for PERC members to remotely participate to PDCO discussions
- joint EMA/FDA early paediatric interactions within paediatric cluster, with issuing a common commentary,
- to jointly organise EMA/FDA workshops with the first one on paediatric pulmonary arterial hypertension to take place in June 2017 at the EMA.

FOLLOW-UP:

- Highlight the recent achievements, e.g. closer interactions between EMA and FDA, experience with common commentaries and pilot with joint early interaction
- Upcoming workshop on PAH, co-organised by EMA and FDA and Health Canada
- Follow-up review of the alternative options proposed for facilitating engagement with EMA and FDA on paediatric developments

Initiatives concerning optimising the dialogue for paediatric medicines development

Industry's reflections to optimise paediatric development focused on three points:

1. Better identification of the paediatric needs

2. Clear and predictable understanding of the references framing discussion on PIPs

3. Improving efficiency of PIPs without changing the timing of the PIP submission through better scientific and regulatory dialogue.

The proposals by industry stakeholders included potential ways forward to identify paediatric needs with a multi-stakeholder approach as one potential basis for agreeing Paediatric Investigation Plans including the possibility to include more specifically the mode of action. The latter is one of the concepts already included in the current reference to frame the definition of the scope of PIPs which participants representing industry considered useful but also in need of revision to include experience gained since its publication. It was discussed that any such initiatives cannot be seen in isolation and indeed there have been first discussions at the PDCO to explore further methodologies for defining paediatric needs. In this respect it was discussed to include the experience with the current inventory of paediatric needs as well as with ongoing multi-stakeholder activities such as 'Accelerate' in paediatric oncology and the 'International Neonatal Consortium' in neonatology.

In addition to the experience with the early interaction (see above) the EMA presented further initiatives to increase scientific dialogue. The PDCO is increasing collaboration with other committees to support the medicine's lifecycle, from early development to marketing authorisation and beyond.

Collaboration with Scientific Advice is ever increasing with PDCO members included in almost all scientific advice procedures relevant to paediatric development. In 2016 there were 142 paediatric scientific advice procedures out of a total 582 and PDCO members were involved in 138 of them. There are dedicated sessions to discuss these during the PDCO plenary.

Recently, the agency is exploring ways for the PDCO to increase collaboration, dialogue and discussion with the CHMP at committee level on topics of common interest based on ongoing procedures at either the PDCO or the CHMP. This is at early stages yet; it is intended to enhance understanding of the work and optimise usage of expertise from both these committees.

FOLLOW-UP:

- Review of the outcome of EC consultation and subsequent initiatives
- Reflection on proposals regarding inventories and identification of paediatric needs

Closing remarks

This platform meeting covered a number of topics across the spectrum of R&D support activities, each of them with a specific focus. For this first meeting a wide selection of topics was identified, given the variety of initial topic proposals and the needs for updates. This was intended to stimulate the debate and to foster identification of areas that need more in-depth exchange.

The discussions highlighted the importance of addressing R&D product support activities in a holistic and integrated manner. Efforts should be made to view such product support for a project level.

In terms of communication, EMA highlighted an improved landing page for development support on the website (see link here). To better structure the access to key information the following is now published in a comprehensive table: main procedural advice and guidance for medicine development; opportunities to interact with EMA during the development of a medicine.

In a post-meeting survey the participants' feedback confirmed the relevance of the scope of this platform. The topics on the agenda were appreciated both in terms of selection as well as delivery, with the most frequent rating on relevance and clarity in either good or excellent. The concrete output from this meeting was appreciated, together with having a detailed list of follow-up activities presented at the end of the meeting. Numerous proposals for future topics were made and the majority of attendees preferred a biannual occurrence of such R&D support platform.