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Human Medicines Research and Development Support Division

Highlight report of the 2nd industry stakeholder platform on research and development support

15 November 2017

Role	Name
Chair:	Michael Berntgen
Present:	Industry: **AESGP** Andrew Thornley, **EBE:** Virginia Acha, Simon Bennett, Isabelle Clamou, Agnes Legathe, Maria Pascual, Sonja Pumpluen, **EFPIA:** Victoria Kitcatt, Anja Langeneckert, Genevieve Le Visage, Mark Joseph Root, Tina Taube, **EUCOPE:** James Barnes, Lars Hyveled-Nielsen, Jens Peters, Maren von Fritschen, Martine Zimmermann, **EuropaBio:** Christiane Abouzeid, Florence Bine, Emma Du Four, Alexa Hunter, David King, Davide Marchi, **Vaccines Europe:** Joao Duarte, Stephane Callewaert, Adam Heathfield, Claire Hill-Venning, Geert Preuveneers EMA: Enrica Alteri, Michael Berntgen, Corinne De Vries, Kristina Larsson, Ralph Bax, Marie-Helene Pinheiro, Jane Moseley, Thorsten Vetter, Emilie Desfontaine, Jordi Llinares Garcia, Zahra Hanaizi, Paolo Tomasi, Valerie Johnson, Lise Flaunø HTA: Chantal Guilhaume (HAS), Anja Schiel (NOMA)

This was the second 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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Parallel Consultation with regulators and HTAs

A. The first experience with the newly launched Parallel Consultation platform

EMA and EUnetHTA presented on the background, and current EU level landscape for advice, what had happened since launch in July 2017 as well as general principles for engagement and several key messages. In particular EUnetHTA provided clarification on the prioritisation criteria and fees.

The activity of parallel consultation with EMA and EUnetHTA is underpinned by the HTA Network reflection paper on synergies between regulators and HTAs, and also features in the workplans of the respective participants. In summary, parallel consultation is a new platform, forming one gateway for all procedures for advice/dialogue, and provides for centralised HTA recruitment, with the Early Dialogue working party identifying and prioritising a subset of requests for consolidated HTA advice involving the Early Dialogue working party.

For all parallel advice/early dialogue procedures, there are now streamlined logistics, and greater HTA coordination. Parallel consultation is a multi-stakeholder, with EMA and EUnetHTA equal partners, working together for benefits in patient access and public health. There is respect for roles and remits to facilitate optimised evidence generation for different stakeholders. This activity builds on successes of Parallel Scientific Advice (PSA)and the Shaping European Early Dialogues (SEED). Early experience with Parallel consultation so far is based on a small number of procedures but the evaluation is positive. Both EMA and EUnetHTA encouraged more applications for Parallel Consultation. Continuous improvement in the procedure is the aim, and a feedback questionnaire for Applicants is under development.

Industry reflected that Joint EMA/HTA scientific Advice and separate HTA advice are complementary, because full HTA may comprise aspects, which are not directly relevant for relative efficacy assessments. Industry also considered that early experiences were positive and supported the process as set out in the guidance document. Industry requested more clarity on: the role of EUnetHTA Early Dialogue (ED) Secretariat and the Early dialogue Committee (EDC), systematic monitoring of the model, more guidance on eligibility for the consolidated parallel Consultation process, commitment to dedicated resources and capacity building across HTAs, and subsequent disease area guidance that comprises viewpoints of regulators and HTA following multiple advices in therapeutic areas.

The discussion focused on clarifying the above questions and other proposals for process improvement e.g. for consolidated advices understanding the prioritisation criteria vs EUnetHTA budgetary restrictions. Industry requested that for the face to face meeting, there should be sufficient time to discuss alternative development scenarios and that the List of Issues should be sent to applicants with sufficient time to allow preparation for the meeting. Specific logistics relating to the possible vaccines Parallel Consultations were discussed in particular how to include relevant bodies where HTA are not the concerned party.

FOLLOW-UP:

- Review of experience with the newly launched Parallel Consultation platform to support continuous improvement, also including feedback from applicants to a new to be developed questionnaire
- Follow-up on patient engagement in Parallel Consultation, based on the EMA and EUnetHTA work plan activities.

- Applicants to consider proposing involvement of other decision makers (e.g. payers, NITAGs) in requests for multi-stakeholder consultation, to allow learning from such engagements.

B. Strengthening the prospective discussions on post-licensing evidence generation

EMA presented the expectation of regulators with regard to the role of post-licensing evidence generation (PLEG), the regulatory requests at MAA, PLEGs in Scientific Advice (SA) together with why and how to engage at SA on this topic. The primary concern for regulators is to assess the benefit risk assess throughout the product lifecycle, and that for scientific question on safety/efficacy pre or post launch, it is critically important to have the right study, and high quality timely methods and appropriate data.

Regarding requests made at Marketing Authorisation Application (MAAs), an analysis of post-authorisation studies (PAS) requested between February to October 2016 was presented. Trends were that most PAS were for initial MAAs and in Oncology. They included twelve Specific Obligations, six Post-authorisation Efficacy Studies, three Annex II Post-authorisation Safety Studies (PASS; all registries), and five Category 3 PASS. The breakdown of interventional vs non-interventional trials, ongoing vs new studies is also reflected in the Conditional Marketing Authorisation 10 year EMA report where two out of three of the Specific Obligation studies were ongoing at the time of imposition. Also whilst the majority of the studies had objectives for safety and efficacy, they also included PK and other objectives, and iboth randomised and nonrandomised studies were included.

A number of reviews of PASS, and of registries are available which document the frequency of such requests and the objectives. Notably real world effectiveness is not infrequent as an additional objective. Methodological deficiencies, delayed completion, delayed start, slow accrual, low data quality, or missing data have been identified. Therefore, PLEG can comprise a wide range of study designs and data sources that could benefit from SA and is not restricted to studies on real world data.

SA on PLEG is not a frequent request to CHMP, either as pre-MAA or post-MAA advice discussions. SA presents opportunities for parallel consultations involving other stakeholders in planning PLEG, and is able to involve multiple committees. There are many other good reasons to request SA on PLEG.

In conclusion, PLEG complements pivotal randomised control trial data; and targets some remaining uncertainties. There are gaps in the workability of registries, with scope for improvement in quality and timeliness for post authorisation evidence generation. There is a need for optimisation of PLEG data for quality, timeliness, and access. To progress scientific understanding and acceptability of PLEG (including real world evidence), further applications for scientific advice and qualification procedures are needed in this area from medicines developers.

EUnetHTA defined PLEG as the process of generating post-launch evidence from clinical practice over the cycle of health technology and using it for re-assessment and reimbursement decisions, and reflected that the optimum timing to discuss PLEG is firstly pre Phase 3, and subsequently when HTA appraisals are finalizing. General and specific guidance were identified including a forthcoming tool to assess the quality of registries. EUnetHTA clarified that EUnetHTA will not organise and/or finance the data collection system (registry or other), whilst requests for PLEG are made at national level (part of the national decision process), EUnetHTA can support national decision on PLEG by proposing a common research question or minimum data set, giving advice on methodology (if registry used, assessing its quality for HTA purposes) to reduce differences between national requests regarding non context-specific information.

Industry considered that evidence and insights from real world data (RWD) can be used to improve patients' health outcomes, their experience of care, and the efficiency of the healthcare system. Industry requested clear and transparent guidelines should be developed with regulatory and HTA bodies on the acceptability of RWE and big data analytics to support life-cycle plans and was committed to full transparency of results of RWE studies submitted for regulatory and HTA assessments. Considerations were raised about improving trust and acceptability of RWE, raising the quality and interoperability of underlying data, promoting best practice in methodology and sustainable industry access to data.

The discussion focused on the timing and barriers for seeking SA on PLEG. It is recognised that early discussion on lifecycle can take place before phase 3 but that late discussions may be needed subsequently to further refine the PLEG proposals. It is necessary to understand the potential use and consequences of the data collected in terms of re-evaluation of benefit risk and value. Industry reflected on time and resource restrictions around MAA impeding further interactions on PLEG at this timepoint. For Vaccines, there is a clear need and opportunity for PLEG to be better coordinated.

FOLLOW-UP:

- Further reflections on opportunities for prospective discussion on plans for post-licensing evidence generation, including scope, topics/questions, time points, contributors and expected impact

Recent update of the guidance for Parallel EMA/FDA scientific advice

EMA provided an overview of a recent revision of the General Principles for parallel EMA/FDA scientific advice, which have been published in April 2017 (Revised general principles). This revision provides a clear procedural framework and indicates feasibility without significant increase in procedural burden; the ambition is to achieve convergence. 'Consultative Advice' has been introduced as new tool.

It was noted that parallel EMA/FDA interactions are helpful tools and uptake should be encouraged. Examples for such parallel interactions (either formal parallel scientific advice / qualification advice or through participation as observers) were reviewed. Particular benefit is foreseen in the context of PRIME/Breakthrough dual designations.

FOLLOW-UP:

- Solicit feedback from industry stakeholders regarding the these parallel EMA/FDA tools including follow-up review of experience with the revised process

Learnings with and further improvements of PRIME

EMA presented an update of Learnings with and further improvements of PRIME scheme. This was based on a response to industry stakeholders following the discussion at the anniversary meeting for the implementation of PRIME. The topics covered the eligibility criteria, operational improvements for the eligibility process, as well as aspects of support within the PRIME scheme. The importance of discussion across decision makers with regard to what constitutes an unmet medical need was noted.

FOLLOW-UP:

- Follow-up on the discussions between EMA and EUnetHTA on the concept of unmet medical need, based on their work plan activities.

Publication of the Orphan Maintenance Assessment Report

At the time of marketing authorisation, the COMP re-assesses the orphan designation to see whether the medicine still meets the criteria for orphan status (in line with Article 5(12) (b) of Regulation (EC) No 141/2000 of the European Parliament and of the Council). In particular, the COMP looks at the seriousness and prevalence of the condition and - if other treatments exist - at whether the medicine is of significant benefit to patients with the orphan condition. The maintenance of the orphan designation at time of marketing authorisation grants 10 years of market exclusivity in the EU.

So far a high-level summary of the COMP review has been published in the COMP minutes as well as in a Public Summary of Opinion (PSO). As an expansion of this transparency measure it is planned to start publishing the COMP reports on review of orphan designation at time of marketing authorisation, which is considered of interest to a variety of stakeholders including HTAs and patient organisations. The following is foreseen:

- The COMP reports of review of orphan designation at time of marketing authorisation will be published on the EMA website at the same time and together with the EPAR.
- The Orphan Maintenance Assessment Report (OMAR) will follow a similar procedure as already available for the EPAR with regards to the Commercial Confidential Information (CCI) check.
- Positive and negative reports as well as the assessment report with List of Questions in case of withdrawal will be published.
- A shorter timeline for the CCI check than for the EPAR is envisaged as the OMAR is expected to be not longer than 20 pages.
- The OMAR will replace the currently published PSOs for orphan medicines at marketing authorisation.
- An OMAR will be produced for all orphan designated products at marketing authorisation (first or extension of indication) as of CHMP in October 2017. It is envisaged that the first publication will be in early 2018.

EMA also explained the content of the OMAR which in line with the assessment report will focus on the aspects related to the orphan criteria and specifically the prevalence section and the discussion on significant benefit. Regarding the latter, it was noted that the scientific review of experience with significant benefit has recently been published.

FOLLOW-UP:

- Review the progress and content of OMAR publications at upcoming stakeholder platform meeting.
- Provision of details of the recent publication on experience with significant benefit

Continuous progress in the area of paediatrics

EMA presented the status of some of the PDCO activities in the 2017 work plan. The reinforced cooperation between PDCO and CHMP, on topics of common interest based on ongoing procedures, was highlighted. The ongoing PDCO's reflection on the experience gained in different therapeutic areas was presented, in relation to findings on deferrals in the 10-year report to the European Commission, with an aim to identify gaps and potential solutions to address them. Participants were also provided with a summary of the work achieved in some specific therapeutic areas (such as paediatric oncology,

neonatology or pulmonary arterial hypertension), the main Enpr-EMA activities in 2017 and PDCO's contribution to published EMA or ICH guidelines of paediatric relevance.

Industry presented their view on multi-stakeholder workshops with relevance for paediatrics. While such workshops are welcome, more transparency on the objectives and intended post-meeting actions would be appreciated.

Industry informed EMA about the expected impact of the EMA Decision (CW/0001/2015) on the revised and revoked class waivers, which will come into effect in July 2018. An EFPIA survey on companies' preparedness revealed that a large majority of companies expect an impact on their portfolio, with half of them expecting a high impact, resulting in an increase in PIP/product specific waivers submissions in 2018-2019.

Finally, Industry shared its positive view on the EC's 10-year report on the Paediatric Regulation, and its readiness to engage with PDCO, EMA and the EC and to collaborate with all paediatric stakeholders on further activities as recommended in the 10-year report.

FOLLOW-UP:

- Follow-up on activities to be performed in the context of future action plan following the EC's 10-year report, including proposals for identification of scientific workshops.
- EMA to further disseminate information to stakeholders on the upcoming deadline for the revocation of class waivers (e.g. website).
- Industry to inform EMA of upcoming PIP/waiver submissions plans further to EMA decision on class waivers of July 2015.
- Opportunity for provision of proposals by industry for streamlining of waiver applications in the context of the revocation of class waivers.

Follow up on opportunities for integrated R&D product support

EMA provided an overview of current opportunities for interactions with regulators during the development phase (Research and development). There are a number of opportunities, all with specific remit. It was voiced however that there might be gaps to allow for a more integrated R&D support, which reviews developments from a project perspective rather than the regulatory framework. Therefore, it would be helpful to identify concrete examples that can support any follow-up discussion on potential needs.

FOLLOW-UP:

- Identification of needs for discussions on the planning of development interactions, based on case studies for integrated R&D support, and report back to the platform

Upcoming operational advances in development support: Introduction to "Scientific and Regulatory Evaluation Procedure Support (S-REPS)"

EMA introduced ongoing activities with regard to the implementation of new software and improvements to the processes for orphan designations. A web-portal application plus attachments will replace current PDF and Word form–based submission. Whilst at this stage the change is for the

orphan designation process, the project is the first step in the EMA's wider digital transformation strategy hence if successful the pilot may be extended to other scientific regulatory processes.

It was highlighted that the new system will make full use of a group of controlled terms lists (SPOR). Pre-registration of sponsor (organisation), substance(s), and a "research product identifier" (RPI) will be a requisite before being able to draft and submit applications. The go live' is scheduled for late Spring- Early Summer 2018.

Industry welcomed the development and expressed interest in supporting this project by acting as volunteers to help develop and test the new system from an applicant/sponsor perspective. Nominations will also be sought via relevant Trade Associations and also directly contacting applicants on the current Orphan database.

FOLLOW-UP:

- Opportunity to contribute to the development of the S-REPS tool – Nomination of RA managers with experience in orphan designation submissions

Closing remarks

The second meeting of this platform followed up from the previous discussion with several topics across the spectrum of R&D support activities. The discussions highlighted the importance of addressing R&D product support activities in a holistic and integrated manner. Concrete follow-up activities have been identified, to be carried forward in between the platform meetings.

In a post-meeting survey the participants' feedback confirmed the relevance of the scope of this platform for discussion of several priority topics for the industry. The topics on the agenda were positively rated (good or excellent) both in terms of selection as well as delivery. Numerous proposals for future topics were made and the majority of attendees were appreciative of the planned regular occurrence of this platform also in 2018.