16 March 2022
EMA/714427/2021

Highlight report from the 7th Industry stakeholder platform on research and development support

23 November 2021

Role	Name
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This was the seventh occasion in a series of meetings between regulators and representatives of industry stakeholder organisations to address all areas of evidence generation along the medicine's life-cycle and related product-development support activities, such as scientific advice and qualification, as well as specifics for paediatric and orphan medicines. 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.

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 7th meeting. Of those not in scope of the agenda, the following developments were highlighted:

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- In terms of the practical arrangements regarding (integrated) drug-device combination products under the Medical Device Regulation, the update of the Q&A providing clarifications on requirements for integral, co-packaged and ancillary medicinal substances in medical devices as well as the guideline on quality documentation for medicinal products when used in combination with a medical device were published.
- With reference to the preparation for Companion Diagnostics review under the In vitro Diagnostics Regulation, a procedural guidance on the consultation procedure is under development. For the level of information on assay/CDx in the labelling of medicinal product, the current principles will be applied whilst further experience is being gained.
- The item of assessment of similarity for Advanced Therapy Medicinal Products has been brought to the CAT for discussion.
- A multi-stakeholder dedicated meeting on 'patient engagement' and 'patient data generation' is in preparation for 2022.

Renovating the scientific advice offering along the medicine life-cycle

A. Outcome of the Focus group on the practical application of integrated development support

The Focus group on the practical application of integrated development support collected case examples from PRIME, COVID-19 and other developments which exemplified or made proposals on the application of a set of design principles intended to guide the renovation of the scientific advice and, more generally, of the development support offering, which had been agreed previously (refer to the highlight report of the fifth industry stakeholder platform on research and development support).

Most examples or proposals related to the design principles of orientation/stewardship, i.e. the existence of a person or function at EMA who could help developers navigate through and utilise successfully the various regulatory interaction opportunities; agility, i.e. the diversification of the scientific advice offering so as to adapt to the variety of developments both temporally and in terms of complexity and multi-decision-maker integration, i.e. the existence of parallel consultation mechanisms between medicine regulators and other decision-makers, such as Health technology Assessment (HTA) bodies or medical devices regulators.

Industry associations proposed the creation of a development (support) Product Lead available for consultation on an ad hoc basis for regulatory and scientific queries, able to communicate promptly and informally with the developer, guiding through the EU interaction opportunities, involving relevant EU regulatory network stakeholders and sharing knowledge among them thus serving as regulatory institutional memory. They further proposed agile and iterative interactions with Rapporteurs using more flexible background documentation and temporally adjustable to the intended interaction depending on the type of product and request. In relation to HTA bodies, there were proposals for increased HTA engagement, process simplification, shorter timelines and higher alignment between regulatory and HTA body recommendations. As far as other decision-makers were concerned, proposals were made for CTFG engagement in EMA scientific advice to facilitate clinical trial approval and for formalisation of interactions with medical device regulators and National immunization technical advisory groups (NITAGs) to support drug-device combination, companion diagnostic and vaccine development and approval, respectively.

Industry proposals also called for mechanisms to support regulatory institutional memory which could involve Scientific Advisory Group (SAG) consultations and a closer collaboration particularly between the Scientific Advice Working Party (SAWP) and the EMA Paediatric Committee (PDCO), publication of Q&A documents reflecting 'current regulatory thinking' on evolving topics of interest to convey regulatory guidance in an expedited way, enhanced and more targeted patient involvement in scientific

advice, collaborative science-making across stakeholders in targeted areas such as ATMPs and continuation of the enhanced regulatory public communication seen with COVID-19 treatments and vaccines.

The EMA addressed the issue of increased scientific advice workload in the second half of 2021. Surges in submissions in May, June and September 2021 led to delays in the start of scientific advice assessment procedures, with developments in the anti-infectives and vaccines area and ATMP developments with questions in the pharmaceutical quality area being the most commonly affected. Mitigation measures included adaptations in the SAWP membership from usual member turn-over and prioritisation of requests based on the time of the submission. In order to improve predictability regarding procedure start in 2022, the EMA will prioritise scientific advice requests more strictly based on the time of the submission with the exception of requests for PRIME products, which will be prioritised by default.

The EMA presented additional preliminary reflections from ongoing SAWP discussions partly prompted by the increased scientific advice workload. SAWP members support a revision of the scientific advice public guidance to clarify submission requirements and scope of scientific advice towards prevention of inappropriate or less meaningful requests which simply add to the workload without producing material benefit. They further support a more seamless transformation of the submission briefing document into the assessment reports used in the course of the procedure and the final outcome document, a review of procedural timelines and steps towards carefully increased flexibility and they call for prioritisation criteria to optimise assessment resource utilisation with the current scientific advice procedural delays and postponements.

FOLLOW-UP:

- Based on the outcome of the Focus group discussions and the SAWP discussions, EMA to establish an implementation plan for actions related to strengthening the scientific advice offering, with consultation with industry stakeholders on selected topics and report back at the next R&D platform as well as other forums (e.g. conferences).
- To further support developers in best usage of central scientific advice, EMA to progress improvement of relevant material (e.g. guidance, manuals, one-pagers).
- EMA/SAWP to pursue short-term measures to address current capacity challenges in scientific advice and provide relevant updates to industry stakeholders.

<u>B. Future proofing the framework for qualification of novel methodologies</u>

Scientific and technological (digital, artificial intelligence, nanotechnology) advances offer multiple innovation opportunities and increase the need for qualification of novel technologies for drug development. Qualification is the only tool to ensure European regulatory acceptability of such novel technologies. Based on experience so far, a review should be envisaged to improve and strengthen the process, in line with the recommendations of the EMA Regulatory Science Strategy (RSS) to 2025.

Preliminary industry proposals for improvements to the qualification process included clarification of scope and integration of qualification with scientific advice, process optimisation so that it becomes more iterative and less costly, involvement of additional ad hoc experts, relevant associations and medical societies based on the nature of the qualification as well as of patient representatives, adherence to procedural timetable to avoid delays, implementation of clear rules to allow regulator participation in public-private partnerships, clarification of intellectual property rules for qualification opinions, improvement of public consultation and of stakeholder interactions, international collaboration with other medicine regulators and involvement of HTA bodies and Notified bodies.

The EMA acknowledged the need for review of the qualification process but challenged the view that this has remained under-utilised and referred to increasing numbers of qualification applications in recent years in line with similar increases in scientific advice requests. EMA further argued that increased flexibility to allow iterative interactions, which is normally not foreseen in the current qualification process, would necessarily lead to extension of timelines and was the main reason for the delayed finalisation of the longest historical qualification procedures.

FOLLOW-UP:

- Establishment of a Focus group to review and strengthen the framework for qualification of novel methodologies. Deliverables would include a horizon scanning of types of methodologies for qualification in the future to inform necessary optimisation steps and an in-depth review of the design principles presented at the platform. The discussion should inform a workshop tentatively planned for mid-2022.

C. Relaunch of Joint Scientific Consultation involving EMA and HTAs

EMA and EUnetHTA21 provided an overview over the past experience with parallel consultations (scientific advice) by regulators and HTA bodies. The modifications to the interaction during Joint Action 3 were revisited and the most recent changes for the latest iteration, the Joint Scientific Consultation, were presented including the amended selection criteria. Practical next steps for the Open Call were presented. Challenges and room for improvements of the parallel consultation were discussed including the preferred format of interactions, the demand for a sufficient number of parallel consultations available as well as the optimal use of the time during discussion meetings.

FOLLOW-UP:

- Review of experience with the first call for parallel EMA/HTA Joint Scientific Consultation at the R&D platform in mid-2022, ahead of the second call planned for October 2022.

D. Follow-up on scientific advice for continuous innovation in known molecules

In follow-up to the discussion at the 6th platform meeting in June 2021, two case examples of known molecule developments were presented. One did not benefit from EMA scientific advice due to the perceived administrative burden of the process, while the other one received multiple scientific advice and clarifications. Industry proposals included to allow "spin-off" and iterative advice, branching off the main scientific advice request; align scientific advice with payers and notified bodies data requests; expand scientific advice provision to better cover use of RWD/RWE; provide the option of receiving integrated regulatory advice in scientific advice processes.

EMA reiterated the invitation for direct discussion with the EMA scientific advice office how specific upcoming requests could be most optimally managed.

Review of the PRIME scheme: learnings and opportunities

Representatives from trade associations gave a presentation on the cross-industry experience with the PRIME scheme, summarising the feedback gathered from 45 companies, by means of a questionnaire. This questionnaire was designed to be complementary to the Agency's one and to capture industry's views on PRIME, also from companies without PRIME experience. The key value drivers for companies, main advantages of the PRIME scheme, reasons for not considering or applying for PRIME as well as key takeaways from the Industry survey were presented. Strategic recommendations to address the value of PRIME and practical aspects to explore were also covered.

The survey results indicated high interest in the PRIME scheme, and of the 25 companies without PRIME experience that responded, none indicated lack of interest as a reason for not having applied.

PRIME is routinely considered by companies to support an expedited development strategy and 69% of companies have it under active consideration for a product.

The main current value of PRIME was seen as the early rapporteur appointment and the provision of a dedicated EMA contact point, to assist navigating the vast array of scientific and regulatory support avenues available at the EMA. The lowest scoring aspects in that survey were regarding the HTA evidence package generation and the facilitation of global development, highlighting the need to strengthen the PRIME scheme to better support these areas.

This presentation was followed by a presentation from the Agency, covering the high-level findings from the 5- year analysis as well as first reflections on possible areas for enhancement of the scheme. The high-level findings from the 5-year analysis focussed on the main findings in terms of surveys to companies with PRIME products as well as the main areas identified by companies for improvement of PRIME. The preliminary findings in terms of experience with PRIME products that have gone through regulatory evaluation process were briefly presented.

The Agency highlighted that the aim going forward would be to maximise effectiveness of support provided to PRIME products and to consider actions to facilitate the work of the rapporteurs in the run up to MAA, including knowledge building and access to up to date information. Overall, it seems important to have an effective exchange to guide the development of products, build knowledge through an agile process and reach a mature evidence package as basis for the thorough review of the later marketing authorisation application.

FOLLOW-UP:

- Publication of the EMA report on the 5-year experience with the PRIME scheme, scheduled for Q1 2022.
- Once established, follow-up discussion with industry stakeholders to support implementation of recommendations to further enhance the value of the PRIME scheme.

Outcome of the Focus group on the concept of an 'evolutionary' PIP

This Focus group was established following the progress report of the EMA-EC paediatric action plan at the 5th Industry stakeholder platform on R&D support in November 2020. Representatives from industry trade organisations and from PDCO and EMA explored the concept of an 'evolutionary' Paediatric Investigation Plan (PIP) including the further development of key elements to define agreed measures in PIPs in 8 teleconferences and provided an interim status report at the 6th Industry stakeholder platform on R&D support in June 2021.

The objective was 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 discussing, on a scientific basis and in compliance with the regulatory requirements, possibilities for and limitations of such PIP model that allows to develop along with the evolution of scientific knowledge. The proposed 'evolutionary' model developed from merging various models discussed (see report) focussing on using the current processes enhanced by a supporting framework with options for integrated dialogue e.g. with PDCO, SAWP, ITF and/or in a multi stakeholder approach as required.

Based on illustrative examples criteria for the identification of paediatric developments that would qualify for a stepwise approach to agree the binding elements in the PIP were proposed. These included not fully characterised mechanism of action, tumour/tissue agnostic therapies, gene therapies, use of extrapolation or innovative trial designs, 'first in disease' and paediatric only developments, programs encountering challenges e.g. with standard of care or due to scarcity of patients. Discussions however showed that these criteria might apply to a majority of proposed

paediatric development programs. It was agreed that this would require a scientific case-by-case discussion with appropriate justification in order to avoid a 'tick-box' approach. This will be further reflected and refined.

Whereas there is already some experience with concepts for planning milestones on the basis of available evidence with the commitment for further interaction, the discussion on the further optimisation and streamlining of key elements to define agreed measures in 'evolutionary' and regular PIPs focussed at an exemplary level on clinical studies and requires further discussion.

The analysis of risks included that such a model might need to a delay in paediatric development and therefore e.g. would require an early PIP submission and furthermore resources potentially gained by a reduced number of modifications of an agreed PIP might be needed for increased dialogue activities which still might be a more beneficial investment.

It was concluded to integrate the outcome of the Focus group into discussions with the EC with respect to the review of the paediatric legislation and to work at PDCO level as well as in a new Focus group on details of the concepts developed and their implementation e.g. in a pilot.

FOLLOW-UP:

- Establishment of a new Focus group to support implementation of the generated concepts. Deliverables would include providing input into the preparation of the pilot for the concept of an 'evolutionary' PIP and developing further the review of guidance particularly on key elements for a PIP.
- Integration of outcome into discussions with the EC on the review of the Paediatric Legislation.
- Discussion and work at PDCO level with a view on developing a pilot.

Progressing the integration of Real-World Evidence into medicines development and evaluation

A. Update on the Big Data Steering Group workplan

EMA provided an update on the progress of delivering the work plan, which builds on the recommendations made in the Big Data Task Force final report and its vision: *By delivering the vision of a regulatory system able to integrate Big Data into its assessment and decision making, we can support the development of innovated medicines, deliver life-saving treatments to patients more quickly and optimise the safe and effective use of medicines through measurement of a products performance on the market.* The workplan contains 10 detailed recommendations for RWE use in human medicines regulation and an additional set of veterinary recommendations.

Key achievements include the launch of the procurement for the DARWIN EU® Coordination centre, procurement for a consortium to deliver a data quality framework, defining a list of metadata for RWD, the finalisation of a data science curriculum and a workshop on AI methods. Additionally, use cases for RWE use in EMA committees' decision making were developed and a multi-stakeholder Learnings initiative workshop was held. Further deliverables include the update of the ENCePP RWE methods guide, BDSG recommendations on ethics advice, adoption of the Data standardisation strategy and progress on the RWE Collaboration Roadmap with FDA and a multi stakeholder forum on Big Data. In terms of veterinary medicines, a workshop on the Veterinary Data Strategy was organised.

EMA also provided further details on the work on discoverability of data sources, whereby a catalogue with metadata describing the main characteristics of the data source will be developed in 2022, building on the ENCePP Resources database, as well as on the development of an improved catalogue of observational studies, building on the EU PAS register. The DARWIN EU® network will be established

in 2022 as a federated network of data, expertise and services, with a central role for is Coordination centre to establish and maintain the network, including to onboard/maintain data sources and to manage the execution of scientific studies. Potential use cases for support of EMA committee decision making include informing about the design and feasibility of planned studies, representativeness and validity of completed studies, disease epidemiology, clinical management & drug utilisation, effectiveness and safety studies and impact of regulatory actions. Benefits of the RWE initiatives include better decisions based on better evidence in drug development and authorisation, as well as optimising the use medicines. Better RWE submissions, the ability to contextualise information provided, and better understanding of evidentiary value will result in a higher acceptance of RWE in marketing authorisation submissions, with time and cost savings. When legal obligations are placed on multiple companies having a marketing authorisation for a particular substance (e.g. generics), studies conducted by the network could help avoiding duplication and reducing cost. Continued engagement and collaboration with stakeholders will be necessary in 2022.

FOLLOW-UP:

- Stakeholders will be kept updated on the progress of delivering the workplan and dialogue on RWE use will continue through future stakeholder platform meetings.

B. Real-world evidence (RWE) to aid decision making during the life cycle of non-prescription medicines

Industry provided reflections on the use of RWE for decision making on non-prescription medicines. It was stated that compared to prescription-only medicines, there has been little focus on the potential role of RWE for non-prescription medicines. Challenges are that non-prescription medicines are purchased without prescription, electronic health records and insurance claims data are not routinely available, and that information on the real-world use of non-prescription medicines is largely uncaptured. Several practical examples from the published literature were outlined where RWE did provide relevant evidence for decisions on non-prescription medicines. It was concluded that a different approach to RWE is needed for non-prescription medicines. In this context patient-generated health data (PGHD) is an emerging source of RWD and could be explored to generate RWE.