European Federation of Pharmaceutical Industries and Associations

EFPIA reflection paper on integrated R&D product support along the product lifecycle

Executive Summary

In the rapidly evolving landscape of medicine development an iterative, responsive and holistic regulatory dialogue with greater flexibility in the delivery of scientific advice and better alignment across stakeholders is needed to reflect the changing pace and process of innovation along the development continuum (i.e. including the post-approval phase). The use of an iterative responsive regulatory dialogue should remain optional but should be available to all products for which this is wanted or considered needed. It should not preclude the possibility to obtain separate advice from stakeholders if this is considered beneficial. Taking note of other ongoing initiatives of both medicine developers and regulators, EFPIA has identified three key requirements for such a future system. These requirements are discussed in more detail below but can be summarised as follows:

A future iterative, responsive regulatory dialogue concept should have:

1. Provide orientation - Ease of advice navigation and alignment of the EMA committees and relevant other stakeholders. An optional first interaction opportunity is introduced to enable orientation and stewardship through the different advice possibilities, identify anticipated complexities and the need for specialized expertise in an early stage.
2. Adapt process – An optimized process is needed to receive rapid feedback or to discuss cutting edge technologies requiring (iterative) expedited dialogue to avoid delays in development or accommodate specialised input for specific types of complex products. Within the same process different types of interactions need to be accommodated, as this may differ from product to product and across time.
3. Enable continuum - An institutional memory of previous interactions and agreements is essential as interactions become more frequent and involve multiple and variable stakeholders (multiple EMA committees, National Competent Authorities (NCA) e.g. in CTA, Health Technology Assessment (HTA) bodies/payers, patient representatives).

A technical solution is needed which allows the relevant Committees/stakeholders/experts to engage as needed and where (contradictory) views across decision makers can be shared in a safe environment. This solution should safeguard confidentiality of information.

Introduction

This reflection paper outlines the EFPIA perspective on a future concept of voluntary iterative, responsive regulatory and scientific dialogue within the EU regulatory framework through the entire medicine lifecycle. A continuum from early development to post-licensing is critical to ensure robust integrated evidence generation. Within the reflection paper, proposals are made as to how such a concept might work within the current legislation, by building on existing tools and incorporating other stakeholders into the regulatory dialogue at the appropriate timepoints.

Early iterative and flexible engagement with regulators and other decision makers will enable clear understanding of the development plan and alignment on evidence generation. It has the additional advantage that it provides regulators and other decision-makers with early awareness on upcoming developments and technologies. Adaptations to the current interaction options are essential to meet the needs of stakeholders for the following reasons:

1. **Complexities within the EU regulatory framework**: Multiple opportunities for interaction have evolved over the years and can involve numerous committees within EMA, different National Competent Authorities, regulators from different jurisdictions and HTA organisations/payers. This multi-stakeholder environment with multiple layers of legal responsibilities (EMA cross-committee decision-making, National responsibilities in decision-making e.g. in CTA, downstream decision-making for reimbursement) is increasing in complexity, raising the potential for inconsistent advice and expectations in addition to making the system difficult to navigate for all parties, adding time and resources on all sides.
2. **Complexities in medicine development:** Scientific and technological advances have enabled the development of therapeutically promising but increasingly complex medicinal products, such as Advanced Therapy Medicinal Products (ATMPs), products which may include a device component or products with a diagnostic biomarker. In this setting, medicinal product development often involves more than one manufacturer (device, diagnostic, medicine). Furthermore, to avoid development delays and ensure timely access to innovative healthcare solutions, manufacturers explore ways to maintain an efficient development process by using novel methods of data generation, such as complex clinical trial (CCT) designs (80% of EFPIA companies have already used CCT designs to collect clinical data[1]), modelling and simulation, real world data (RWD) and real world evidence (RWE), innovative manufacturing and analyitcal technologies as well as progressive Chemistry/Manufacturing/Control and Good Manufacturing/Distribution Practice strategies. A smooth integration of multiple evidence types in one dossier to support regulatory approval needs to be agreed with the stakeholders.

In this rapidly evolving landscape an iterative, responsive regulatory dialogue with greater flexibility in the delivery of advice and better alignment across stakeholders is needed to reflect the changing pace and process of innovation along the development continuum. In this regard, useful experience is already available from special programmes such as the PRIME scheme and the adaptive pathways to patients concept which create the conditions for an interative dialogue at key development milestones involving additional stakeholders next to regulators.

Furthermore, EMA's Regulatory Science Strategy (RSS) 2025 (published March 31, 2020) identifies the need to 'Diversify and integrate the provision of regulatory advice along the development continuum' as an important goal. The importance of an integrated approach is emphasized by the fact that several other objectives from EMA's strategy paper touch on the same topic (e.g. PRIME, development support for precision medicines, how to foster innovation in clinical trials, for a full overview please refer to 'Analysis and summaries of public consultation of the RSS 2025'). EFPIA, representing key stakeholders (users) of the scientific advice system, rated this recommendation as 2nd top priority. In 2019, EMA created a focus group including EMA, individual company (incl. Small & Medium Enterprises) and Trade Association representatives to consider how scientific advice could be better integrated to support most efficent development and to develop principles to guide implementation of EMA's RSS 2025 via respective EMA committees work programmes (ongoing).

[1] Source: EFPIA Leaflet Standing Still Is Not An Option. Take Action With The Regulatory Road To Innovation

In parallel, those aspects reflected in the EMA RSS are also consideredin the European Medicines Regulatory Network (EMRN) strategy, foreseen to be finalized end of November after a stakeholder consultation. This demonstrates that integrated Scientific Advice along the development continuum with engagement and alignment of all relevant stakeholders is considered a priority action, both for EFPIA and regulators.

EMA has recently published two scientific articles emphasizing the importance of early interactions as an opportunity to improve the generation of evidence required for bringing innovation to patients, focussing on the generation of post-licensing evidence[2] and on the use of new digital technologies in medicines development programmes[3].

EFPIA's recommendations are aiming for an all encompassing approach from early development to post-licensing and also take into account additional activities, such as:

- EFPIA is currently developing Dynamic Regulatory Assessment (DRA) proposals. DRA is an umbrella concept attempting to fully link iterative regulatory dialogue with ongoing data submission and evidence assessment enabled by novel IT capabilities. An iterative regulatory dialogue is a critical part of a successful DRA.
- Early health authority interaction is proposed to achieve a more efficient and tailor-made approach in paediatric development. In these proposals (developed by EFPIA's paediatric working group), paediatric development dialogue should be integrated and function within a single-entry platform such as iterative stakeholder dialogue.
- EFPIA's Reflection paper on PRIME is assessing current experiences of medicine developers with PRIME, providing an impact assessment of each step and aims to define the value of an 'ideal' PRIME. Iterative, responsive regulatory dialogue is an important element of PRIME in its current and future state.
- EFPIA notes the importance of connecting its recommendations with adequate resourcing including capability and capacity building to support implementation. (for details, reference is made to the position of EFPIA's fees working group, which is currently under discussion).

Recommendations from EFPIA

EFPIA's recommendations address three key requirements for a future iterative, responsive regulatory dialogue concept which should be optional but available to products for which it is wanted or considered needed. Although it is presented as one single concept, it should also be possible to make use of parts of the concept (e.g. the alignment of advice across EMA committees and NCA for clinical trial applications will be applicable to more products than the need for frequent advice).

1. Provide orientation - Ease of navigation and alignment of the EMA committees and relevant other stakeholders.
2. Adapt process.
3. Enable continuum - An institutional memory of previous interactions and agreements.

Ad 1: Ease of navigation and alignment of stakeholders

A future iterative, responsive regulatory dialogue concept will involve multiple EMA committees (particularly PDCO, COMP, CAT, SAWP, QWP, PRAC and CHMP, inspectors, PAT team), different NCA (including clinical trial authorization bodies and CTFG members), Notified Bodies, HTA organisations/payers and regulators from different jurisdictions (countries, regions). It is also important to assess in an early stage when and how patient input in the regulatory dialogue is indicated.

The optional use of a first interaction opportunity for each project to determine its complexities, through a single point of entry will facilitate navigation (saving time and resources on all sides),

[2] Moseley J, Vamvakas S, Berntgen M, Cave A, Kurz X, Arlett P et al. Regulatory and health technology assessment advice on postlicensing and postlaunch evidence generation is a foundation for lifecycle data collection for medicines. Br J Clin Pharm 2020;86(6);1034-51. https://doi.org/10.1111/bcp.14279

[3] Cerreta F, Ritzhaupt A, Metcalfe T, Askin S, Duarte J, Berntgen M, Vamvakas S. Digital technologies for medicines: shaping a framework for success. Nature Reviews Drug Discovery 2020;12 May. doi: 10.1038/d41573-020-00080-6

interconnection across the EU network and alignment across all relevant stakeholders. A suitable technical solution will additionally support this concept.

This first step in the interaction process for a particular medicine in development would be to define in an early stage the type and amount of supportive dialogue that is expected to be needed (see also under 'Ad 2. Adaptable process'), i.e.:

1. To proactively identify scientific, legal and regulatory issues.
2. To identify the need for specialized expertise.
3. To agree on an optimal milestone-driven interaction schedule and identify which committees/stakeholders/experts are expected to be needed at what point based on the identified complexities.

To ensure reliability in downstream decision making, the output resulting from the interaction should be aligned across EU committees and NCA and other stakeholders as relevant (e.g. CTFG, Notified Bodies, HTA, independent experts). The use of a virtual environment where the relevant Committees/stakeholders/experts engage may facilitate the sharing of views across decision makers and contribute to achieving alignment. This environment should safeguard confidentiality of information. A coordinating body should ensure the efficiency of the process and ensure an optimal balance between sound scientific discussion and rapid feedback as needed.

EMA's current Innovation Task Force (ITF[4]) remains of importance and interactions should be part of the holistic safe-harbor discussion along the development continuum.

Ad 2: Adaptable process

EFPIA strongly supports EMA to create a rolling dialogue across the product lifecycle, with different levels of regulatory engagement based on the attributes of a particular product. The process should be optionally available for those products where it is wanted and needed.

The current EMA scientific advice process follows a defined process, which may not be suited for all forms of interaction that may be needed or beneficial in an iterative, responsive regulatory dialogue concept. Examples of adaptations that would be desirable include the following:

- Rapid feedback may be needed on how to best handle questions for which no formal advice or clarification is needed. For this, it would be important to establish appropriate conversation possibilities.
- Expedited, multi-stakeholder dialogue may be required for cutting edge technologies or novel methods, in order to not delay clinical trials in which they are used. These include for example the use of digital endpoints or diagnostic biomarkers. Early interactions could identify areas where relevant expertise is lacking and allow timely involvement and preparation of external experts by EMA. Qualification Advice for novel technologies is of high importance and should be seen as integral part of the scientific advice ecosystem.
- Dynamic and holistic stakeholder dialogue (also considering potential future rolling regulatory assessment) is needed to adaptably accommodate specialized input for specific types of products (e.g. paediatrics, drug-device combination products) and should be considered under the "continuum of regulatory advice" umbrella of the EMA Regulatory Science Strategy to 2025 and the EU Network Strategy. It should be possible to seek timely joint interaction and advice on medicine-medical device combination products by involving notified bodies, inspectorates, NCAs and/or EMA, depending on the questions.
- Mechanisms should be defined for advice on broader and general topics ("Broad Scientific Advice" concept).

Next to EMA-coordinated advice, the option of complementary national scientific advice in one or several (Simultaneous National Scientific Advice) countries should be part of the available options, including as a mechanism to define an optimal question for the EMA scientific advice. The availability of an iterative, responsive regulatory dialogue concept should not preclude the possibility to seek separate advice from other stakeholders.

[4] EMA's Innovation Task Force (ITF) in its current setting aims is to make regulatory support for medicines developers that is currently available at national and EU levels more visible and attractive to innovators. One of its objectives is to establish a discussion platform for early dialogue. Its principles, if applied more broadly, fit well within our current proposals.

The following conditions are important for consideration when developing this adaptable process:

- Relevant stakeholders as defined in the previous section should be included.
- Preliminary stakeholder feedback ahead of meeting allows sponsors to prepare and suggest additional topics for discussion based on this feedback.
- Interactive approach during the procedure with face to face or video conference interactions for key discussions and allowing greater access to specialized working groups when novel approaches are proposed. This should include CMC, quality and manufacturing which may be in need of informal, swift input from regulators.
- Flexible timelines for emerging issues or follow-up questions.

Ad 3: An institutional memory and strong continuum of previous interactions and agreements

The collaborative, multi-stakeholder and adaptable process described in ad 1 and 2 should be supported by clearly defined requirements and guidelines on product development.

Given the time-span elapsing between early interactions and the start of the regulatory and market access approval processes, and the potentially many different stakeholders involved, it is essential that good institutional memory of all agreements and guidance on a particular development is maintained. A robust platform (e.g. cloud based) is needed for submission of supportive data, storage and safe harbor information exchange. This would enable a transparent exchange of information, data and views, while taking particular care to safeguard confidentiality for all stakeholders as interactions take place in different stages of development[5]. In time, a well-designed system would build knowledge, becoming an institutional memory for all involved stakeholders. In this respect, the relevance of the EMA telematic strategy is highlighted as it aims to optimize support to the EU regulatory authorities.

Points for further discussion with scientific advice stakeholders

- How to ensure a balance between transparent exchange of information, data and views, while taking particular care to safeguard confidentiality as interactions take place in different stages of development?
- What are the user requirements for a technical solution to facilitate discussions, data sharing while maintaining confidentiality (tools, access)?
- Are further changes needed to ensure or strengthen the provision of advice where other important stakeholders (e.g. Notified Bodies [such as devices, in-vitro diagnostics, companion diagnostics], GMO competent authorities, Radiation Protection/Nuclear Medicine national authorities) are involved?
- As an initial goal aligning across EU stakeholders is key. If successful in the EU, how could alignment with other jurisdictions (countries, regions) be obtained?

Enabling features for 'iterative, responsive regulatory dialogue'

To support all above recommendations, it is recognized that optimal resourcing options including possible adjustments to funding models may be necessary. For up-to-date details on specific EFPIA resourcing and funding proposals, reference is made to EFPIA's Fees Working Group.

A staged introduction with an expansion of eligible products over time can help to manage resource requirements.

The recent example of the pandemic COVID-19 challenges emphasizes the importance of pro-active measures and time-efficient interactions and offers another good learning tool for a future system.

[5] For current EMA policy and output on access to documents please refer to https://www.ema.europa.eu/en/about-us/how-we-work/access-documents#public-documents-section

A pilot would be useful to better determine how to enhance support in a more holistic fashion in line with the above recommendations.

This paper illustrates how some relatively minor modifications to the current approach, within the current legislative framework and EMA structures and procedures would make a significant and positive difference to the development of medicines and innovative technologies. We would welcome an opportunity to discuss this work further with relevant stakeholders.