value added medicines

a medicines for europe sector group

Scientific Advice for Continuous Innovation in Known Molecules

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RECOMMENDATIONS FOR THE OPTIMISATION OF EMA SCIENTIFIC ADVICE FOR VALUE ADDED MEDICINES DEVELOPMENT

Executive summary

Continuous innovation, i.e. the development of so-called Value Added Medicines, consists in improving and optimising existing off-patent medicines to address unmet medical need and provide patients, healthcare professionals and payers with additional therapeutic options that may be better suited to their needs. This strategy is an important complement to the discovery of new chemical or biological entities.

Companies opting for a continuous innovation approach would benefit from scientific advice that better accounts for the specificities of this strategy.

The following key changes to EMA scientific advice can make it better suited to the needs of developers applying a continuous innovation approach:

1. Increase the flexibility of scientific advice processes by including "spin-off" requests branching from the initial questions and introducing an agile approach.

2. Align EMA scientific advice with data requests from HTA, payers and notified bodies along a common thread and make European scientific advice interoperable.

3. Update and expand the scope of scientific advice to better cover use of Real World Data and Real World Evidence.

Continuous innovation builds on existing treatments to deliver improved medicines

In the development of medicines, healthcare benefits can be delivered in different forms. They can be achieved through the discovery of a new chemical or biological entity, but they can also be accomplished by continuous innovation, building on existing medicines to deliver further benefits for patients, healthcare professionals and/or payers. Medicines developed with a continuous innovation approach are known as Value Added Medicines (VAMs).

VAMs have the potential to address unmet medical needs and can be developed with multiple strategies:

- **Repurposing**: identifying new indications for an existing medicine.
- **Reformulation**: changing the dose and/or route of administration of a medicine to reach new patient populations (e.g. paediatric patients) or to improve the safety and/or efficacy of a medicine in the existing indication and patient population.
- **Combination**: creating new fixed dose combinations of existing medicines to simplify therapy regimes or combining a known molecule with a device, service, or digital app.

While traditional innovation approaches can lead to breakthrough discoveries and are established innovation strategies, continuous innovation is increasingly emerging as an important complement to them, thanks to its potential to address unmet medical needs and deliver benefits in a timely, sustainable, and cost-effective way. The repurposing of dexamethasone to treat COVID-19 patients in the ongoing pandemic

showcases the potential of VAM development to provide life-saving treatments[1].

VAM development strategies differ significantly from the R&D steps associated with traditional innovation approaches, which generally entail a longer development timeline, a larger budget and extensive demonstrations of safety and efficacy. Since continuous innovation strategies start from well-established medicines, they can build on pre-existing evidence of the safety and efficacy of the molecules, including real world data gathered through years of use of a medicine in patients.

Scientific advice can inform VAM manufacturers on how to best drive medicines development forward

When wanting to add a new product to their portfolio, manufacturers routinely ask regulators questions to explore which is the most appropriate way to generate robust evidence on a medicine's benefits and risks. This is done through a formal process known as scientific advice. In Europe, scientific advice can be provided by the EMA as well as other National Competent Authorities.

Based on the differences between breakthrough and continuous innovation approaches, developers applying a continuous innovation strategy will have specific needs in their requests for scientific advice. In line with the EMA guiding principle of supporting research and innovation to stimulate the development of better medicines[2], this paper aims to facilitate the optimisation of scientific advice for VAM developers, by identifying key practical improvements that can be implemented to make the current scientific advice better suited for continuous innovation, without compromising on the high quality of EMA scientific advice.

1. Águas, R., Mahdi, A., Shretta, R. et al. Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. Nat Commun 12, 915 (2021).
https://doi.org/10.1038/s41467-021-21134-2
2. EMA final programming document 2021-2023
https://www.ema.europa.eu/en/documents/report/final-programming-document-2021-2023_en.pdf

How to optimise EMA scientific advice for continuous innovation

The Value Added Medicines Sector Group of Medicines for Europe has identified three key areas for EMA scientific advice optimisation. Experts from the Group have formulated recommendations addressing the most pressing issues and, whenever possible, the proposed strategies are backed by examples showcasing how change could benefit developers opting for continuous innovation strategies.

1. Increase the flexibility of EMA scientific advice processes

When asking for scientific advice from EMA, manufacturers can pose questions that fit into one of the following categories: quality, non-clinical aspects, clinical aspects, and methodological issues. Questions on regulatory procedures (e.g. on selecting the most appropriate regulatory pathway) are covered separately. After the questions are submitted, a formal process following rigid timelines is started by the regulator to provide scientific advice.

In some cases, the rigid structure and timelines of this process become problematic. This happens for example when the initial advice received prompts new questions that fall into different categories from the ones that were initially selected or when a company may wish to modify a scientific advice request that is currently being processed. Both instances require companies to initiate new and separate rounds of scientific advice, which is highly inefficient in terms of time commitment and resource allocation.

The current structure of this process also allows for a limited number of set interactions between EMA experts responsible for providing answers and the company seeking advice. These interactions can only occur at pre-specified time points over the course of the scientific advice process.

The inefficiencies highlighted above are particularly problematic for VAM developers, as their budgets are often more limited than those allocated for de-novo development and timelines for continuous innovation are generally tighter, meaning that the impact of delays is greater.

Proposal for improvement

To address these inefficiencies, we propose that greater flexibility is embedded in the EMA scientific advice process.

A more flexible scientific advice process should include "spin-off" requests branching from the initial questions. This would increase efficiency in those instances where new and separate questions are raised by the advice received or new information becomes available to the manufacturer while EMA experts are still in the early stages of formulating their recommendations. **Better integration of questions that concern regulatory procedures would also help companies in making fully informed decisions on their development processes**. Such an iterative, integrated, and flexible approach would lead to a better use of time and resources and yield a leaner process overall. Moreover, **rather than following a rigid stage-by-stage timeline, an agile approach should be sought whenever possible**. Sub-groups of EMA experts working in parallel on specific aspects of the questions received would achieve quicker responses and could potentially meet and interact more easily with the manufacturers when clarifications are needed from either of the sides. Avoiding a "packed room" meeting in favour of more frequent and focused interactions is a further means to improve efficiency. This system would optimise the use of time and resources through more direct exchanges and a reduced administrative burden.

Adopting a more agile and integrated process, that enables spin-off scientific advice requests, focused interactions between companies and experts, and an iterative approach to scientific advice provision, would allow EMA to better address the continuum of evidence generation, in line with the goals set in the EMA regulatory science strategy to 2025[3].

3. EMA regulatory science strategy to 2025
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

CASE STUDY 1

Seeking clarifications on scientific advice received required multiple separate questions, resulting in significant further use of company resources

Company A submitted multiple rounds of scientific advice requests for product X. Each request was prompted by the results of the ongoing development of product X but had to be submitted as a new and separate filing rather than as part of an ongoing exchange with the regulatory agency.

In two separate instances, the scientific advice received from EMA required one or more clarifications as insufficient detail was provided in the feedback given. Examples of the necessary clarifications included confirming the acceptance limit for a specific impurity, confirming the possibility of submitting additional data at Day 121 (i.e. after the formal end of the scheduled advice process and during assessment of the Marketing Authorisation Application) and obtaining further details on a protocol proposed by regulators.

Each request for clarification had to be submitted as an additional question, rather than as a simple follow up branching off the main scientific advice request.

This instance well exemplifies how allowing spin-off and iterative scientific advice centred around the initial request for product X would have resulted in a simpler and more comprehensive advice provision, with less administrative burden.

CASE STUDY 2

Excessive administrative burden prevented an EU-based company from seeking scientific advice from EMA, contributing to a VAM only being marketed in the US and not in the EU

EU-based Company B developed a reformulated VAM, product Y. Throughout the course of the development of product Y, the Company requested scientific advice from FDA, where several concatenated and iterative requests of scientific advice for the product could be submitted. Some of these requests were even accompanied by a clarifying conference call with the FDA and no extra costs were incurred when subsequent requests were filed. All were connected to the initial request and addressed with an iterative approach and therefore they did not require a separate procedure.

The administrative burden and lack of flexibility associated with the current standard scientific advice provision prevented Company B from seeking scientific advice from EMA, as it was foreseeable that multiple rounds of advice would have been necessary, each requesting a stand-alone separate procedure.

In this case, the lack of flexibility in scientific advice provision contributed to the decision of Company B to only seek regulatory approval for their product in the US. Commercial considerations were also factored into Company B's decision.

CASE STUDY 3

Separating scientific and regulatory advice negatively impacted a Company, due to lack of coordination in the provision of information from the two separate streams

Company C was developing a combination VAM aimed at simplifying therapy regimens and intended to be sold as a combination pack in which part of the content consisted of fixed-dose combination product XY and part was a monotherapy with only one of the active substances of product XY.

The company simultaneously sought both scientific and regulatory advice for their intended VAM. The scientific advice issued supported the proposed clinical development plan, prompting the company to further pursue the development of this VAM. However, several months after having received a favourable response for its scientific advice question, Company C received a partial answer to its regulatory question, submitted at the same time as the scientific advice request, stating that no regulatory pathway was available for its product. Based on this information, the company halted the ongoing development programme.

While this particular instance was characterised by an undue delay in the compilation of the regulatory advice response, it highlights how better alignment between the provision of scientific and regulatory advice could help companies to make fully informed decisions in the early stages of their development programmes.

2. Align EMA scientific advice with data requests from HTA, payers and notified bodies along a common thread and make European scientific advice interoperable

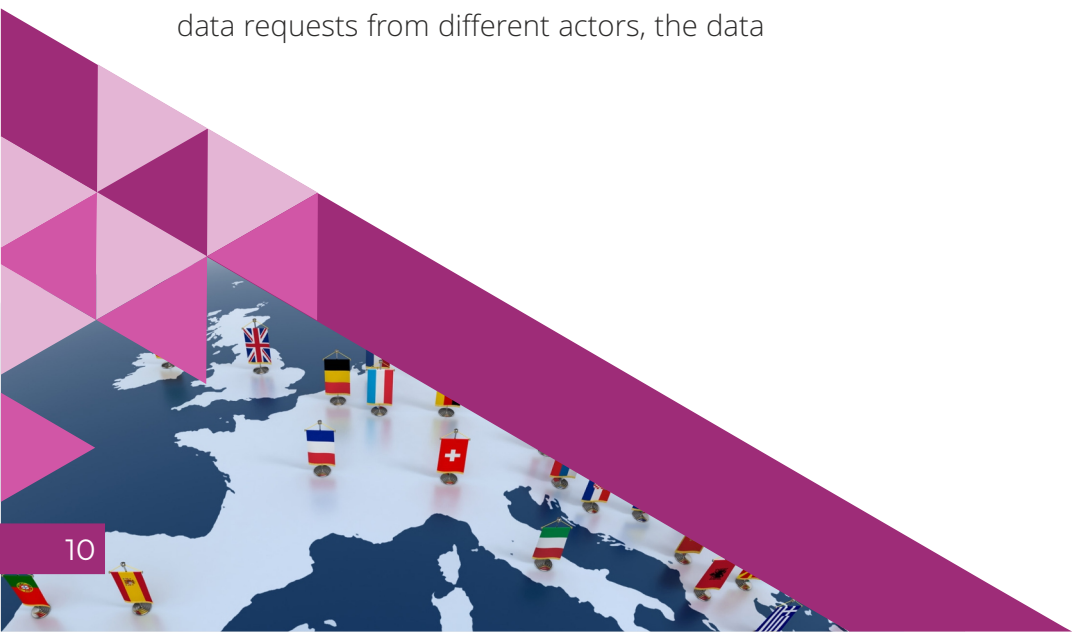
Even after regulatory steps are cleared, there are still many factors that contribute to a company's decision on whether to market a VAM or not and its ability to do so.

Typically, as well as submitting data to the regulator, a manufacturer will have to negotiate the medicine's price with payers from different regions and occasionally submit further data to Health Technology Assessors (a process known as HTA) and Notified Bodies (NB). During some or all of these steps, manufacturers can be asked to submit data pertaining to their product, as done for regulatory purposes.

When there are significant discrepancies in data requests from different actors, the data generation process becomes burdensome and expensive, which can be particularly problematic in the case of VAMs, for which development budgets are generally more limited than for medicines developed with traditional innovation approaches and profit margins may be relatively small.

Uncertainty on pricing negotiation outcomes also makes it difficult for companies to make informed decisions about whether to market a medicine in a given region, particularly when the scientific advice they receive from a local regulator points towards an expensive development programme.

On top of the complexity arising from data generation requests pertaining to different steps of a medicine's development, a similar problem may be observed when companies request scientific advice from a European regulatory authority (EMA or a National Competent Authority), but then decide to apply to a different one to receive a marketing authorisation. In this case, there is a risk that the manufacturer may be asked to submit different evidence from that suggested through scientific advice.



Proposal for improvement

To avoid discordant data requests among regulators, HTAs, payers and/or notified bodies and maximise the efficiency of early-stage development of VAMs, all relevant stakeholders should be involved in the scientific advice process.

The EMA PRIME scheme provides an example to build on for the implementation of this suggestion, as it already enables different stakeholders to align their data generation requirements when scientific advice is requested.

To formally ensure that the scientific advice received from all European competent authorities (EMA and NCAs) is valid and "interoperable" in case the company which requested it goes on to submit a marketing authorisation application with any national regulator of an EU member state, it should be explicitly stated that scientific advice received from all EU regulators, while not legally binding, should be officially recognised and considered by EMA and European NCAs.

Achieving better coordination in data generation requests is in line with the EMA goal of bridging from evaluation to access through collaboration with payers[4] and is also highlighted as a means to improve the availability and accessibility of medicines in the EMAN strategy to 2025[5]. Parallel assessment by regulators and HTAs is listed in the European Commission's Pharmaceutical strategy for Europe as one of the actions that can help address unmet medical needs[6].

The EMAN strategy to 2025 also lists developing consistency and convergence in scientific advice between national authorities and exploring further synergies with HTA bodies and payers (building on the success of parallel scientific advice procedures) as a means to foster and promote innovation in the EU[7]. Formal recognition of the interoperability of scientific advice, requiring that it is considered by all European regulators, would represent an important milestone in achieving this goal.

4. EMA regulatory science strategy to 2025
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
5. European medicines agencies network strategy to 2025
https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf
6 Pharmaceutical strategy for Europe
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN
7 European medicines agencies network strategy to 2025
https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

CASE STUDY 4

Lack of early engagement with payers and HTA bodies during EMA scientific advice contributed to a Company's decision to not seek regulatory approval for a VAM in the EU

Company D developed VAM product Z, initially intended for launch on both the US and EU markets. Therefore, during the development of product Z, scientific advice was sought both from FDA and EMA.

FDA scientific advice proposed to conduct a clinical trial with a test and a placebo arm, which is the established approach in the US. On the other hand, EMA scientific advice rejected this study design, requiring a comparator rather than a placebo arm, following the applicable clinical efficacy and safety guidelines from the EMA.

Due to the approach proposed by the EMA being more onerous, a business case for the launch of the product in the EU could only have been built if pricing discussions and HTA evidence generation requests had been included in the scientific advice.

Because, during the scientific advice request, no coordination was available to evaluate the impact of non-regulatory data generation requests or determine whether potential pricing conditions could justify the more expensive clinical development approach from a business perspective, Company D decided to only market product Z in the US.

While it is impossible to know whether engagement of non-regulatory stakeholders at the scientific advice stage and early pricing discussions would have led to a sufficiently compelling business case for launching product Z on the EU market, better coordination between regulators, HTAs and payers during this scientific advice request would have surely allowed company D to make a better-informed strategic decision.

3. Update and expand the scope of scientific advice to better cover use of Real World Data and Real World Evidence

One of the basic premises of VAMs is that they deliver improvements of well-established medicines, based on the needs and use experience of patients and healthcare professionals. It follows that the starting point of the development of a VAM is always an existing medicine, for which extensive data will have been collected by the time the VAM development process is initiated. This information, which is collected outside of clinical trials, is defined as Real World Data (RWD). The evidence derived from it is called Real World Evidence (RWE).

In Europe, despite rapid progress and a strong effort by EMA in progressing on RWD and RWE, clear guidance on the use of this type of data is not yet available. This makes scientific advice on its use of paramount importance. However, there is a recognised shortage of expertise on these topics among regulators and currently this type of evidence is not well covered by questions that can be asked as part of scientific advice requests.

Proposal for improvement

Scientific advice on the use of RWD and RWE should be clearly integrated in the EMA provision, with the aim of ultimately designing a framework for the assessment of these data and clarifying what are the necessary requisites for the use of RWD and RWE in continuous innovation. Appropriate training to develop internal expertise on these topics among regulators will be essential to successfully apply this recommendation.

Allocating resources towards better RWD and RWE scientific advice provision is in line with the EMA's goal of promoting the use of high-quality real-world data in decision making[8] and would enable greater clarity in the use of these data.

8. EMA regulatory science strategy to 2025
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Why it is important to optimise scientific advice for continuous innovation

VAMs have the potential to address unmet medical need and improve the quality of treatment for numerous patients with faster and more affordable development compared to traditional novel medicines. VAM development differs from the traditional pharmaceutical development in both the level of pre-existing evidence and the process (timelines and budget). Streamlined and efficient scientific advice provision, that better caters for the needs of developers applying a continuous innovation approach, will contribute to making these important medicines available to patients.

More generally, the strategic importance of improving the scientific advice provision to evolve the EU regulatory framework and to make it fit for its purpose is recognised in the EMA regulatory science strategy to 2025[9], the EMAN network strategy to 2025[10] and the EMA final programming document 2021-2023[11]. In turn, regulatory efficiency is highlighted in the Pharmaceutical strategy for Europe as a prerequisite for a modern pharmaceutical system[12].

In conclusion, the practical strategies suggested in this paper, if implemented, will contribute to the promotion of sustainable continuous innovation approaches in the EU through increased regulatory efficiency. The case studies backing these suggestions highlight the potential of these improvements to make Value Added Medicines more broadly available to European patients, unlocking significant benefits not only for them but also for healthcare systems across EU member states.

9. EMA regulatory science strategy to 2025
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
10. European medicines agencies network strategy to 2025
https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf
11. EMA final programming document 2021-2023
https://www.ema.europa.eu/en/documents/report/final-programming-document-2021-2023_en.pdf
12. Pharmaceutical strategy for Europe
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN

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