Commentary on the Draft EMA regulatory science strategy 2025

Date of release: 28 Jun 2019

Contents

Commentary

EMA has set an ambitious path for regulatory science to 2025, following the fast pace of innovation in developing novel complex medicines, setting objectives towards creating a new regulatory framework that will support innovation throughout medicines development.

While it is important to foster innovation and shape the regulatory science to be able to support novel therapies entering the market, we see **further opportunities** of translating regulatory science and innovation into patient access by **ensuring that regulatory pathways which support the life-cycle of innovation are in place in time to enable a multi-source environment** when the market exclusivity is over.

Off-patent medicines have a track record in opening and broadening access to medicines. Ensuring a fit-for-purpose regulatory environment for multi-source products is a key enabler to realising EMA's mission "to promote and protect the health of those it serves through medicines regulation. This means ensuring that both

Rue d'Arlon 50 - 1000 Brussels - Belgium
T: +32 (0)2 736 84 11- F: +32 (0)2 736 74 38
www.medicinesforeurope.com

people and animals in Europe have timely access to medicines that are safe, effective and of suitable quality, as well as the information needed to use those medicines and make informed choices about their treatment.''[1]

Innovation brings value to healthcare systems by providing new therapy opportunities to the patients. At the same time, cost pressures on healthcare systems in the EU from innovation are increasing, especially with further developments in the oncology, orphan and advance therapy medicinal products (ATMPs) sectors. The evolution of the market is putting additional pressure on the off-patent sector calling for lean/cost-efficient development and manufacturing of off-patent medicines.

To ensure that advances in the innovation and regulatory science are truly translated into greater patient access, there is a need to build an understanding of how this translates into market access to the medicines and the potential influence on competition.

To help the off-patent sector remain a sustainable and valuable part of healthcare systems, ensuring equity of access to all medicines, it is important to:

- **Keep in mind that a multi-source environment requires different approaches and speed to innovative medicines.**
- **Learn actively from the system by optimising EU processes and infrastructures, create fit-for-purpose requirements and risk-based approaches taking into account the available body of evidence (prior-knowledge, real world data), and ensuring regulatory consistency.**
- **Ensure coordinated global regulatory science and regulatory policy advances.**
- **Actively prepare the regulatory framework for the upcoming "life-cycle of innovation": e.g. targeted therapies (non-blockbuster) oncology, orphan medicines, ATMPs.**

Given the importance of our sector in Europe (currently 70% of prescribed medicines are off patent) we would like to see an ambitious and dedicated strategy, supporting the EU network's readiness for future development and access to off-patent medicines. There is a need to nominate one dedicated body/platform to put in place a more coordinated holistic off-patent medicines policy, taking into consideration early on the specificity of follow-on products and covering all aspects from development to marketing authorisation, post-licencing maintenance and market access interplay (similar to i.e. orphan, paediatric, biosimilar, herbal medicines).

The number of off-patented medicines undertaking centralised regulatory procedures is growing, and already represent a broad majority of the de decentralised procedures. There is therefore a need for the entire EU Regulatory Network (EMA, HMA, CMDh) to elaborate its strategy with a clear focus on the off-patent sector.

What we recommend:

In general, for the next 5 years, it is strategically important for the EMA to allocate proportionate efforts on optimisation of existing procedures and processes, as well as the regulatory science advances where experience and prior knowledge is important.

We would like a dedicated off-patent medicines platform/dedicated body and contact point within the EMA.

[1] EMA Regulatory Science Strategy 2025 - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Recognising opportunities for optimisation in the existing systems

Optimisation of existing regulatory pathways could further benefit European healthcare systems, by releasing resources where scientific and technological advances allow for optimisation, leveraging years of experience and tailoring to the specific product needs. Not only industry resources, also medical authority resources can be re-invested in "unknown" territories by streamlining the processes in place.

Optimisation in the off-patent medicines development process

- We welcome the agency recognising the need for earlier and more frequent dialogue to foster development, improving trial designs and avoiding unnecessary trials in patients/healthy subjects while maintaining appropriate safeguards. We encourage the agency to clarify or define **data 'thresholds'** – e.g. what is the data that needs to be generated by the sponsor in order to make meaningful **scientific advice** possible. We also encourage EMA to build further on tailored scientific advice to support step-by-step development of new biosimilar medicine candidates as well as value added medicines with known active substances.
- We propose to further develop the biosimilar framework for tailoring the clinical part of the development, where we see the biggest potential for efficiency gains, driven by regulatory sciences, with advantages for developability, patient access and healthy biosimilar competition. Such efficiency gains would also enable biosimilar competition for biologics where efficacy powered confirmatory studies are not feasible or too costly, due to complexities in the clinical application, limitations in patient recruitment, challenges for targeted biologic medicines with smaller population sizes (i.e. non-blockbuster). Increasing capabilities in physicochemical analysis and, more importantly, recent improvements of the in-vitro functional characterisation toolbox may create additional opportunities to waive confirmative efficacy/safety trials, in some cases even with the absence of a qualified pharmacodynamic marker. **We support the adoption of ambitious risk-based approaches in the planning and development of biosimilar clinical comparability trials, which reflect product and patient related factors**. Towards the end of 2019, we will be providing a thorough analysis of the evidence and experience available in the EU and the international context on this topic as a basis for a dialogue with the regulatory authorities.
- Technology that supports clinical trials comes not only in the form of methods of data collection (such as wearables) and new endpoints, but also as alternative approaches complementing clinical trials or as **novel technologies that support the running infrastructure of traditional trials**, such as electronic consent forms, communication with electronic health records, etc. These technologies can have a positive impact on the efficiency of classic clinical trials and should also be part of the EMA priorities.
- Reduction in the number of Clinical Trials should be made possible with **the harmonisation of requirements for bioequivalence studies**. Once harmonisation is achieved, companies will be able to develop one formulation to market globally avoiding different studies in different regions, putting human subjects through unnecessary and thus unethical experimental trials, and increasing time and cost for bringing products to market and creating barriers to entry for smaller markets. Regulatory science shall support the evidence and the **acceptability of a single**

bioequivalence study carried out using the Comparator Product authorised by a stringent regulatory authority. Results from a pilot study on the indirect comparison of reference products from different markets (based on data from bioequivalence studies) are expected to be available in 2020 Q1/2. These results could be used to discuss the methodologies for acceptance of foreign reference products under the scope of single global development of generic medicines.

- Furthermore, we welcome the initiative to **validate new tools to demonstrate bioequivalence of complex generic products**, which could potentially decrease the cost of development and advise the agency to investigate further into the optimisation of the regulatory framework. An example of an innovative approach of successful implementation in the US is the approval of generic glatiramer acetate without any supporting clinical study. This links into the need for harmonisation of regulatory requirements to allow for global development of a product to allow faster access for patients to generic medicines**. Off-patent medicines could be a learning opportunity on gathering evidence through real-life use data and modelling, simulation and extrapolation** - as there is already a lot of data gathered on quality, manufacturing, safety and efficacy.
- Overall, we would **encourage EMA to work on international convergence** and develop global standards together with other agencies as an enabler to the optimisation of the development of off-patent medicines for multiple jurisdictions.

Optimisation in the authorisation and post-authorisation phase

- We support EMA in **developing competence and expertise in the field of complex products that combine medicine and a medical device**. This type of product is not solely reserved for the innovative medicines sector but is also common in generic, biosimilar and value-added medicines development. Furthermore, single integral products (Medical Device Regulation, MDR, Article 117) should be expressly included and the scope should not be limited to complex products since non-complex products will also benefit from these measures, in the light of changes brought about by the implementation of the MDR.
- The **current regulatory framework for the lifecycle management of medicinal products needs to evolve to better reflect scientific and technical progress and ensure operational efficiency** in line with the objective of Better Regulation. Experience gained since the last amendment of the variations framework in 2008 presents an opportunity to move to a more adaptable, proportionate and optimised approach that better supports innovation and life cycle of medicines. Such changes have the potential to facilitate continual improvement, reduce manufacturing delays and mitigate supply issues. Furthermore, developments in new information technology (IT) systems provide the opportunity to incorporate efficiency and innovation in the variation management system freeing-up regulatory capacity to enable a greater focus on those changes that may impact on quality, efficacy or patient safety, with consequent benefits to public health.
- The industry is currently working on case studies showing the factors which have influenced the maintenance of the medicinal products over last 10 years , taking account of the technological and scientific evolution. Industry will also provide examples where the current EU regulatory system to report the changes to the MA constitute a barrier rather than a support in bringing

updated information and innovation to products on the market in a timely manner. Those case studies are expected to be ready in III/IV Q 2019.

The evolution of the maintenance of medicinal products shall better reflect advances in science and technology as well as the practical implementation of the risk-based approach:

- To accommodate better knowledge and experience gained with a risk-based approach for well-established biological products.
- To recognise continuous improvement of and a new approach to manufacturing optimisation (ICH Q12, ICH continuous manufacturing, Q14).
- To benefit from significant progress in digitalisation and from an availability of tools and IT solutions revolutionising data collection and processing.
- To implement a new approach to life-cycle management of the supply chain by changing the way of informing about the changes to supply chains/ making a more risk-based distinction between elements to be included in the dossier (and reported via variations) and those covered by GMP and audit principles (or eventually reported via SPOR only).

- **The European pharmacovigilance system** is one of the opportunities for EMA to showcase what has already been built in gathering real world data and to further build on. We should explore ways to maximise the use of the system and improve its efficiency. In this area, the value of new technologies could also be explored. The principle of the 3S (smart, strategic, selective) should be emphasised.

Optimisation of the IT infrastructure, backbone of the Regulatory system (Telematics)

The effective use of IT systems can be a powerful enabling tool for regulatory efficiency across Europe. Several benefits could be achieved by maximising the opportunity of the SPOR database and the concept of the Target Operating Model (TOM), by moving towards electronic product information (e- leaflet) and by building on the success of CESP (Common European Submission Platform) to harmonise and make redundant national portals. There is a major opportunity by linking systems and making multiple use of databases to accelerate procedural efficiency, accuracy and at the same time remove redundant infrastructure. **We recommend avoiding multiple standards and different Telematics tools and systems across Europe that can generate unnecessary complexity and impede trusted access to information, restricting the flow of data between authorities, industry and patients.**

- **Holistic approach to Telematics programmes:** interdependency and connection of different IT Systems as the main drivers; there is a general tendency to work in silos on different Telematics projects. This implies the duplication of data submissions and a huge increase of administrative burden for regulators and industry in keeping data consistent and reliable in centralised and national databases. The regulatory system should anticipate the change in data generation and knowledge management. This requires harmonisation and optimisation of future business processes and current and future Telematics systems. We recommend adopting common and harmonised standards as well as a holistic approach to Telematics systems across Europe. The implementation of different systems for the same regulatory purposes can generate unnecessary complexity and impede trusted access to information, restricting the flow of data between authorities, industry and patients. Therefore, we recommend using a holistic and harmonised approach to all on-going and future Telematics projects with a focus on data quality, interoperability and inter-dependency of Telematics projects, when needed.

- The future telematics strategy should also provide a strategic view of moving from a document-based review towards a structured data-based review. Our long-term vision is that regulatory submissions should be paperless (enabled by the removal of any national requirements), with a direct exchange of structured-data between Industry and Agencies. Ideally one single communication channel should be foreseen. Improving interconnection between EMA, NAs and MAHs via digitalisation and submission and re-use of structured data is essential to support better outcomes and efficiency in the Regulatory network.

The implementation of the Target Operating Model (TOM) for ISO IDMP is critical for the use and acceptance of the data elements and processes. For TOM implementation, the entire process, from development, registration, to placing the product on the market, including the prescription phase, should be analysed, discussed and agreed with Industry Stakeholders. This programme should be a priority for Regulators and Industry. Achieving a more agile regulatory Telematics system will improve the efficiency of the Regulatory network with the final goal being to improve public health for the benefit of patients.

Optimisation in shortages management, medicines availability

- We strongly support EMA in the objective to increase availability of medicinal products in the EU. **EMA should have a stronger focus on leading and championing the exchange of information on medicines shortages**. The agency is the privileged entity that has access to information that competitors do not or rather cannot have. For that, it should take the lead in connecting information on the market and manufacturing, improving the management of shortages.
  EMA should clearly state the need for harmonisation of definitions and procedures regarding availability at European level. Regulatory incentives for established, but essential, generic medicines should be considered and promoted as a strategic decision to the National Competent Authorities (NCAs).
- Unavailability is not related solely to shortages, there are many contributing factors. Where urgent actions are required to be taken in the supply chain (e.g. non-compliance of manufacturer), Medicines for Europe is looking towards a more **transparent discussion between inspectors and Marketing Authorisation Holders (MAHs)** and having transparent mitigation plans for both regulators and MAHs to take firm and risk-based decisions.
- We should avoid potential regulatory barriers that could contribute to shortages. Regulatory science should contribute to a more scientific/risk-based approach to Environmental Risk Assessment (ERA), instead of applicability to all products in the same way and independently of their impact on the environment (high/low risk). **The recommendation for a risk-based approach to ERA** and the need for more detail on ERA Waiver of Requirement for ERA Studies for Generic products should be taken into careful consideration to avoid high costs of repeat ERA studies with no value-added benefit to either the patient or the environment, as well as the creation of guidelines on sharing the data among different MAHs.

Communication with the healthcare community stakeholders

- While the EMA 2025 strategy looks towards improving regulatory frameworks and communication towards stakeholders, it lacks assertiveness. A lot was done in the past to put Europe at the forefront of regulatory science and in terms of creation of communication tools

and videos on regulations, pharmacovigilance systems etc. We recommend further strengthening confidence in the existing regulatory framework, reassurance of the system's quality should be reinforced and acknowledged throughout the strategic paper. The strategic recommendation to promote the availability and uptake of biosimilars in healthcare systems is very welcomed and fits the aim of ensuring patients timely access to affordable high-quality medicines very well. **Further strategic communication campaigns to reinforce trust and confidence of stakeholders is one of the key roles EMA can play.**

- Delivering real-time information in the form of **electronic Patient Information (ePI)** will be of great benefit to the patient. We fully support greater focus on patient engagement by providing real-time/up to date/regulatory approved patient information which is user friendly and understandable and has great potential to improve patient adherence. ePI should also represent a tool which guarantees a stronger connection between all stakeholders. ePI is the **best example to show how regulatory efficiency and empowering patients in the Health system have a common pathway**. As recognised in the EMA key principles document, this programme should "*offer possibilities to streamline, simplify and speed up the regulatory process in the creation and updating process (variation) of Pi, just using existing data of SPOR…both for regulators and the pharmaceutical industry*". The opportunities that ePI could generate in the health system for patients and the whole regulatory network are great. Therefore, the process of delivering ePi is critical. This programme should be designed with other ongoing or future telematics projects in mind. It is important to avoid the risk of starting a new initiative and working in a silo. There is also the high risk of new technology advances by the time of its implementation. TOM and its potential optimisation of the variation process represents a very important stepping stone also with regard to the eSmPC/ePIL/eLabel project. TOM would improve the speed of updating patient information dramatically and reduce the effort for preparation and review by Industry and Agencies, with benefits for all actors involved. The future Telematics Roadmap should include this project and its interconnection with TOM and other linked programmes.

Recognising the need for new operating models to be created/designed

Creating frameworks for life-cycle of innovation

The life-cycle of innovation evolves towards multi-source medicines being supplied once intellectual property, regulatory and market exclusivity periods have expired. The EU regulatory framework continuously evolves, adjusting to emerging challenges and opportunities.

The creation of regulatory pathways that allow a life-cycle of innovation and the increase of patient access to modern therapies, by supporting a multi-source environment once the market exclusivity is over, is key to sustaining healthcare systems.

There is a further need to design regulatory pathways to enable future developments in the off-patent sector in line with future opportunities. High costs of novel therapies are placing stress on healthcare budgets, which we can observe in different areas (e.g. targeted therapies, oncology products, orphan medicines, Advanced Therapy Medicinal Products -ATMPs) and a decreasing number of patients per product are being catered for. Therefore, to further improve access, frameworks need to be established or re-shaped to allow a natural evolution of the innovation life-cycle.

Areas for consideration include, but not are limited to: repurposing of existing active substances (e.g. extending parallel consultation to repurposed medicines), orphan, ATMPs, paediatric, geriatric medicines.

Advanced therapy medicinal products undeniably present a paradigm shift in healthcare. However, the high cost of ATMPs is putting the sustainability of healthcare systems and accessibility of those products under question. In addition to supporting the translation of ATMPs into patient treatments, EMA should also consider developing a regulatory framework that will support a multisource environment of ATMPs that will lead to a competitive market and affordable therapies in the future.[2]

The off-patent medicines development and registration paradigm is different from that of New Chemical or Biological Entities. (NCEs, NBEs) and requires fit-for-purpose designs.

What we recommend:

The EMA should include the development of clear multi-source registration requirements and incentives (where needed) for all innovations as a strategic pillar to achieve EMA's objective in terms of better access to all medicines.

As an example, the design of a fit-for-purpose set of requirements and a registration pathway for off-patent targeted medicines (including orphan medicines) (chemical or biologic) should be developed urgently, with a short-term objective, given that authorised targeted (including orphan) medicines are ALREADY becoming available for multisource developments without the regulatory requirements to establish equivalence or comparability being feasible/applicable in this context.

In the longer-term, learning from the orphan multi-source experience, a multisource ATMP framework will need to be established.

Operating strategy to combat antimicrobial resistance (AMR)

One of the biggest healthcare threats to modern societies is AMR and, while we are looking for novel antimicrobial therapies, we should also preserve what we already have.

Some of the older generation of antibiotics that are currently not being used as common first-line or second-line treatments risk disappearing from the market.

To preserve future sources of off-patent antimicrobial agents, we encourage EMA to open a discussion on possible incentives to maintain the marketing authorisations for this very important group of medicines. New systems can help address the global threat of antibiotic resistance by leveraging existing antibiotic products. The

[2] https://onlinelibrary.wiley.com/doi/10.15252/emmm.201809992

recognised global public health threat of AMR already causes 25 000 deaths in the EU[3] and 700 000 deaths globally per year and may cause up to 10 million deaths annually by 2050.[4]

Using existing antibiotics properly is a critical component towards building a lasting strategy to combat AMR. Off-patent and generic antibiotics may be at risk of market exit due to low margins, prescribing behaviours and other factors.[5] Indeed, antibiotic shortages have been observed across the EU and around the world. Some of the oldest antibiotics, often called "forgotten antibiotics," are particularly effective for resistant bacterial infections, but are the most vulnerable to market exit. When prescribers are forced to use suboptimal treatments due to unavailability, it is costlier and may accelerate the development of AMR.[6]

In order to ensure that effective antibiotics are available to address the threat of AMR now and in the future, EMA should:

- develop an evidence-based list of critical off-patent antibiotics with a multi-sector stakeholder group;
- evaluate the potential for a scientific approach to antibiotic cycling or rotation schemes;
- prevent future market exit by providing targeted regulatory relief for MAHs of critical antibiotics. EMA could do this through decreased cost of maintaining authorisations via a reduction in post-approval regulatory fees or an introduction of a special reduced annual fee structure applicable to antibiotics for these vital public health products;
- optimise the regulatory pathway for older antibiotics that have previously been unavailable in some or all European markets and provide incentives by means of a reduction in regulatory fees for Marketing Authorisation Applications; and
- work with the European Commission and member states to create a framework of procurement incentives for off-patent and generic antibiotics such as multi-winner tenders and non-price selection criteria, to ensure a stable supply of highly-effective antibiotics.

Promoting use of prior knowledge and Real-World Data (RWD) / Artificial Intellligence (AI) in the decision-making process

We call for a **proportionate consideration of the strategic use of big data in both the known and unknown territories** to ensure that the progress and optimisation made in the known field can efficiently help redirect needed resources to the great challenges of the unknown.

[3] European Commission. *A European One Health Action Plan against Antimicrobial Resistance (AMR)*. 2017, ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf.

[4] O'Neill, J. (2017). Trends in antimicrobial consumption and antimicrobial resistance, 2000-14. *Tackling Wasteful Spending on Health*. doi:10.1787/9789264266414-graph22-en

[5] Pulcini, C., Mohrs, S., & Et al. (2016, November 16). Forgotten antibiotics: A follow-up inventory study in Europe, the USA, Canada and Australia. Retrieved May 24, 2019, from https://www.sciencedirect.com/science/article/pii/S0924857916303363?via=ihub#bb0010

[6] Tängdén, T., Pulcini, C., Aagaard, H., Balasegaram, M., Hara, G. L., Nathwani, D., . . . Cars, O. (2018). Unavailability of old antibiotics threatens effective treatment for common bacterial infections. *The Lancet Infectious Diseases,18*(3), 242-244. doi:10.1016/s1473-3099(18)30075-6

For generic, biosimilar, and value-added medicines containing well known active substances and being follow-ons from the reference products after expiry of IP rights, it **is very important to consider all existing sources of information and sources of data in the regulatory processes related to known molecules**.

Off-patent medicines producers typically generate a vast amount of information / data on the great number of medicinal product batches they manufacture and release for patient use; all contributing to the collective knowledge of a given molecule. Big data and real-world evidence should be further used to avoid **unnecessary repetition** of studies and generation of data which are already known but may **not** be **sufficiently well collected and analysed.**

Big data is an extremely important tool to transform data into information. The set of recommendations provided in a Big data Task-force report/summary report represents a good starting point to improve regulatory efficiency and the regulatory decision-making process. We also welcome a data-sharing culture that could inspire all the regulatory network and stakeholders involved, with the condition that patients' privacy is protected.

However, to use RWD in the decision-making process, the regulatory environment needs to be prepared to validate and ensure reliability, quality and regulatory compliance of the data.

It is crucial to keep in mind that a **multi-source environment** requires different approaches and a different data source to innovative medicines. This should be a base concept in designing and preparing the decision-making process of the regulatory environment, using the benefits of Big data.

Regulatory consistency will be achieved by learning actively from the system by optimising processes, **creating fit-for-purpose requirements** and **risk-based approaches and** taking into account the **available body of evidence**.

Factoring in the Integration of Artificial Intelligence (AI) to regulatory processes and decision making will be important for the EMA to be future proof.

Our proposal is for EMA to consider piloting the AI involvement in regulatory decision making with an off-patent registration initiative, particularly where tailoring or regulatory science advances would be integrated.

That way progress is made on innovative tools yet with lower risk, well known and understood candidate medicines.

Medicines for Europe

Medicines for Europe (formerly EGA) represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines for Europe, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and R&D sites in Europe, and invest up to 17% of their turnover in medical innovation.