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Contribution to the

REFLECTION PAPER ON THE USE OF ARTIFICIAL INTELLIGENCE (IA) IN THE MEDICINAL PRODUCT LIFECYCLE

EUROPEAN MEDICINES AGENCY

Barcelona, 31 December 2023

Presentation

Faus Moliner Abogados is a modern boutique law firm, specialized in dealing with legal matters typical of the pharmaceutical industry and other companies which operate in the life sciences sector.

Faus Moliner has been recognised as the best law firm in Spain in pharmaceutical law in several international publications.

In 2017, Jordi Faus together with José Vida directed the work "Tratado de Derecho Farmacéutico" published by Editorial Aranzadi, being this the first publication in Spain where a complete analysis has been carried out, from an academic and doctrinal perspective, about the regulation of the medicine's life cycle in Spain.

In 2019, 2020, 2021 and 2023, Faus Moliner was awarded the Expansión Jurídico Award for the Best Law Firm in Health Sciences.

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Barcelona, 31 December 2023

CONTRIBUTIONS

Our feedback to the European Medicines Agency's (EMA) Draft reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle includes to the following general comments:

1. General considerations

The Reflection Paper could be improved by highlighting the need to ensure transparency and explainability through adequate legal documentation frameworks in the fields of regulatory compliance, formal risk-assessment, data protection and mitigation plans. Those should be promoted, even for lower risk uses as a best practice where applicable.

2. Definitions

It is crucial to work towards a common taxonomy at least on the basic theoretical principles to avoid situations in which a system might be considered AI by the EMA and not by other bodies or institutions.

Therefore, we encourage adopting the same definition of AI system that the one in the final version of the AI act, which is likely to be the one proposed by the OECD: "An AI system is a machine-based system that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that [can] influence physical or virtual environments. Different AI systems vary in their levels of autonomy and adaptiveness after deployment.

3. Clinical Trials

We support the approach of the Reflection Paper regarding the need for AI systems used in clinical trials to comply with good clinical practice (ICH E6 guideline for good clinical practice). In our view, those general guidelines can coexist with specific advice on good practices for the most common uses of AI/ML in a clinical trial setting. In addition, we would suggest including an explicit reference to the fact that, when AI/ML systems support clinical trials, data quality standards and metrics shall be well documented in a data quality framework.

AI systems are oftentimes used for patient recruitment. In that context, and particularly considering the processing of the European Health Data Space (hereinafter "EHDS"), there is a need to ensure ethical data use and mechanisms to assess the potential effects of recruitment biases arising from geographical, demographical, or personal characteristics, particularly if the EHDS includes opt-in or opt-out clauses for secondary uses.

AI systems can also be used to predict possible adverse effects, drug-target interactions or for monitoring safety while conducting the clinical trial. The Reflection Paper differentiates mainly between early-phase clinical trials and pivotal clinical trials, but in our view this approach could be improved if the risk allocation depended not only on the stage of the clinical trial, but also on the inherent risk of the use foreseen. For example: the risk of the use of AI/ML to optimize or manage

the design of the protocol may vary depending on factors such as the use of real-world evidence obtained to reassess algorithm correctness or the intent to apply datasets to populations with limited data (e.g. pediatric or rare diseases).

In addition, there are several hurdles when it comes to decentralized clinical trials, one of which is data collection and processing. Since patients are off-site, they must regularly and consciously submit their own participation data. This can bring up issues with patient compliance and data errors. Sponsors, CROs and medical research institutions can leverage AI to solve these issues in several ways. They can create algorithms to analyze patient data and create decisions that will achieve a desired outcome – in this case, consistent patient compliance. AI can optimize and generate notifications that prompt patients to complete electronic clinical outcome assessments (eCOA) for a more reliable data pool. Moreover, AI programs can assist patients in submitting their data by analyzing the quality of the data prior to acceptance. For example, an AI program can evaluate an image to see whether it fits the requirements of the clinical trial. It can then prompt the patient to retake the image with recommendations regarding image quality, such as lighting or angle. This limits the amount of insufficient or substandard submissions, thereby leading to fewer data processing errors.

Also, when AI/ML is used to predict the response of a patient to various interventions, section 2.2.4 of the Reflection Paper on precision medicine should be applicable as needed.

4. Update management in AI systems

AI systems evolve constantly. The process of incorporating new advancements and versions of already existing systems shall be feasible and combine the need to maintain patient safety while not unnecessarily burdening useful innovation.

While it is fully understandable that the EMA does not want to regulate in detail as technology is advancing at a very rapid pace, we suggest developing a more elaborated framework on how to manage updates to existing AI in terms of setting out the level of documentary and training evidence that is going to be required, as well as the procedural aspects of such integration according to a risk-based approach.

5. Product information

The Reflection Paper rightly identifies that the most common risk arising from the use of AI/ML in product information is that models can include plausible but erroneous output.

For its final version to be future proof, the Reflection Paper should also consider possible uses of AI/ML in this field arising from the spread of electronic product information (ePi) as foreseen in the proposal for a revision of the general pharmaceutical legislation of the EU. For instance, if AI/ML models are to be used to process changes in the safety profile of medicines or adapt the product information to the reader, this would trigger risks of errors, biases, and misinformation with potential direct consequences in public health. We would therefore suggest that the Reflection Paper includes considerations on that regard, suggesting best practices as to prevention and collaborates with healthcare professionals particularly on this field.

6. Environmental management

The manufacturing and use of medicinal products has significant impact on the environment. In this regard, the revision of the general pharmaceutical legislation of the EU has identified gaps in the current environmental protection landscape and proposes to strengthen obligations for manufacturers. In particular, the proposal includes pre- (e.g., refusal to grant marketing authorization where the accompanying Environmental Risk Assessment is not adequate or if the risks have not been sufficiently addressed) and post- authorization measures, as well as obligations related to awareness and environmental risk databases, where IA can play a key role as a support for manufacturers (e.g. to calculate environmental impact).

It is desirable that the final version of the Reflection Paper includes a section addressing how AI can support reducing the environmental impact of medicinal products.

7. Collaboration

Collaboration is key in advancing the regulatory framework for the use of AI/ML systems in the lifecycle of medicinal products. Not only collaboration among authorities (EMA and national regulators), but also with stakeholders and particularly with the medical devices sector.

This is particularly relevant taking into consideration that most uses of AI will rely on medical devices categorized as high-risk under the upcoming AI Act (proc. 2021/0106(COD). EMA should at least consider (i) the need for transparency shall be combined with the fact that medical devices do not have the regulatory protection in place for medicinal products so that further investigation and innovation are not deterred; and (ii) the interplay of the medical device conformity assessment with the assessment likely to be conducted under the AI Act, to unify the processes as much as possible to avoid overlaps.

8. Liability regime

The use of AI-enabled products and services in the lifecycle of a medicinal product is not exempt of risks for person in addition to those that a medicinal product may pose. It must be considered that, at the time of this submission, the Proposal for a Directive of the European Parliament and the Council on adapting non-contractual civil liability rules to artificial intelligence (AI Liability Directive) in the pipeline.

The Reflection Paper should consider addressing how the proposed liability regime for damages caused by AI-enabled products and services could impact the lifecycle of the medicinal product. This assessment should be updated as the AI Liability Directive progresses up until its final version.

9. Towards an integrated health ecosystem

The Reflection Paper provides considerations for the use of AI/ML in the lifecycle of medicinal products, including post-authorization. In the current landscape, solutions promoting a

coordinating approach to healthcare while supporting patients to manage their own health are growing rapidly and have a real potential to advance healthcare.

Some legislative proposals are starting to adopt a similar approach. For instance, one of the aspects being considered in the European Health Data Space is the use of data from wearables and wellness applications both for primary and secondary uses. Similarly, the Reflection Paper should also consider the potential of real-world data in patient follow-up considering that this is not a one-size-fits-all model: the risk level might also vary depending on whether AI/ML is used to inform or drive clinical management (lower risk) or to treat or diagnose (higher risk). The Reflection Paper could provide recommendations clustering the most common types of interventions.

Also, AI/ML as well has a potential pivotal role in early-detection of shortages though the use increased available data and AI/ML algorithms

10. Use of AI in supporting the patient journey

At first glance, it might seem like AI used in supporting patients through their journey is linked to healthcare provision and might thus overlap with competences of Member States according to article 168 TFEU.

However, the use of smart inhalers, PROMs systems or AI-integrated EHRs might lead to relevant treatment decisions regarding treatment adherence or even changes in the interventions or dosage. Given this direct impact on the lifecycle of medicinal products, we suggest that the Reflection Paper further explores this area and provides recommendations as to how to integrate these data into post-authorization decisions.

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