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Public consultation on EMA Regulatory Science to 2025

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Introduction

The purpose of this public consultation is to seek views from EMA's stakeholders, partners and the general public on EMA's proposed strategy on Regulatory Science to 2025 and whether it meets stakeholders' needs. By highlighting where stakeholders see the need as greatest, you have the opportunity to jointly shape a vision for regulatory science that will in turn feed into the wider EU network strategy in the period 2020-25.

The views being sought on the proposed strategy refer both to the extent and nature of the broader strategic goals and core recommendations. We also seek your views on whether the specific underlying actions proposed are the most appropriate to achieve these goals.

The questionnaire will remain open until June 30, 2019. In case of any queries, please contact: RegulatoryScience2025@ema.europa.eu.

Completing the questionnaire

This questionnaire should be completed once you have read the draft strategy document. The survey is divided into two areas: proposals for human regulatory science and proposals for veterinary regulatory science. You are invited to complete the section which is most relevant to your area of interest or both areas as you prefer.

We thank you for taking the time to provide your input; your responses will help to shape and prioritise our future actions in the field of regulatory science.

Data Protection

By participating in this survey, your submission will be assessed by EMA. EMA collects and stores your personal data for the purpose of this survey and, in the interest of transparency, your submission will be made publicly available.
For more information about the processing of personal data by EMA, please read the privacy statement.

Questionnaire

Question 1: What stakeholder, partner or group do you represent:

- ○ Individual member of the public
- ○ Patient or Consumer Organisation
- ○ Healthcare professional organisation
- ○ Learned society
- ○ Farming and animal owner organisation
- ○ Academic researcher
- ○ Healthcare professional
- ○ Veterinarian
- ○ European research infrastructure
- ○ Research funder
- ◉ Other scientific organisation
- ○ EU Regulatory partner / EU Institution
- ○ Health technology assessment body
- ○ Payer
- ○ Pharmaceutical industry
- ○ Non-EU regulator / Non-EU regulatory body
- ○ Other

Name of organisation (if applicable):

VPH Institute

Question 2: Which part of the proposed strategy document are you commenting upon:

- (•) Human
- ( ) Veterinary
- ( ) Both

Question 3 (human): What are your overall views about the strategy proposed in EMA's Regulatory Science to 2025?

Please note you will be asked to comment on the core recommendations and underlying actions in the subsequent questions.

The strategy proposed by EMA contains the necessary elements to lift EMA's regulatory science to the level where it can proactively work on innovating the way medicinal products are evaluated, allowing for a more streamlined, safer and cost-efficient process, benefiting all stakeholders.

Question 4 (human): Do you consider the strategic goals appropriate?

Strategic goal 1: Catalysing the integration of science and technology in medicines development (h)

- (•) Yes
- ( ) No

Strategic goal 2: Driving collaborative evidence generation – improving the scientific quality of evaluations (h)

- (•) Yes
- ( ) No

Strategic goal 3: Advancing patient-centred access to medicines in partnership with healthcare systems (h)

- (•) Yes
- ( ) No

Strategic goal 4: Addressing emerging health threats and availability/therapeutic challenges (h)

- (•) Yes
- ( ) No

Strategic goal 5: Enabling and leveraging research and innovation in regulatory science (h)

- (●) Yes
- ( ) No

Question 5 (human): Please identify the top three core recommendations (in order of importance) that you believe will deliver the most significant change in the regulatory system over the next five years and why.

First choice(h)

13. Optimise capabilities in modelling and simulation and extrapolation

1st choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

The EMA (European Medicines Agency) proposed strategy on Regulatory Science to 2025 recognizes the importance of emerging technologies in general and modelling and simulation, also known as in silico methods, in particular. However, the document tends to stress the value of in silico methods almost exclusively in connection with the reduction of animal experimentation. While we agree that this is a relevant application for such methods, it is not the only one and likely not the most impactful one for the patient and for the industry. The term In Silico Trials indicates a number of use cases, not only related to pre-clinical evaluation, but also to the reduction, refinement, and in some cases even replacement of clinical trials. The cost of healthcare is a growing problem. In higher income countries the raising costs associated with the aging population and the resulting greater expectation of care are challenging the financial sustainability of universal healthcare models. In lower income countries the accessibility to pricey new therapies is a major issue. Everywhere, as we are successful in treating the most common conditions, the burden of disease moves to rarer conditions (rare diseases) and to subgroups within common conditions that respond poorly to the standard of care for that disease. All these challenges are quite different from each other, but all share one common factor: the cost of innovation in healthcare is too high and the pace of medical innovation clearly too slow. This has two components: we already harvested all the low-hanging fruits, and now only very complex therapeutic targets are left, for which the traditional “trial and error” approach is falling short. The second is that growing (and fair) social pressure for safer and effective medical products is increasing the cost, complexity and duration of the regulatory process. While there is disagreement on the absolute values, all experts agree that the cost to develop and bring to market a new medical product has been raising exponentially in the last 30 years. In every other industrial sector this problem has been solved by adopting and widely deploying modelling and simulation. From aerospace to automotive, from civil nuclear to chemical and energy industry, the safety and performance of new products, including their regulatory assessment, is done “In Silico”. It is time we pursue the same revolution for medical products.
There is now a variety of predictive technologies for life sciences: bioinformatics, systems biology, computational biochemistry, physiology-based pharmacokinetics, physiology-based and biophysics-based mechanistic models, non-linear system identification methods, Bayesian modelling, Big Data Analytics, and analytical artificial intelligence methods, just to name a few. Each is well suited for a specific class of problems, but all together provide a formidable set of methods, that can be used to develop “In Silico” trials, that can complement, supplement, or in some cases even replace conventional clinical trials.
In Silico Trials could radically change the regulatory process. When new evidences impose more stringent regulatory scrutiny, for example when new adverse effects and failure modes are observed clinically, adding a new safety evaluation would be less demanding than it is now: extending In Silico Trials to evaluate the risk for one additional adverse event is much simpler, cheaper and faster than doing this experimentally. Almost every day regulators worldwide are authorizing in Silico technologies that are directly used in the therapeutic pathway as decision-support systems, through the “software as a medical device” regulatory pathway. If computer models can guide the diagnostic, prognostic, or therapeutic decision for individual patients, why should they not be able to advise on the safety and efficacy of new medical products?
We are convinced that regulators such as EMA must play a key role as In Silico Trials are introduced. Like every disruptive technology it brings promises of drastic reduction in the cost of innovation and the time to market, but also new, and substantially different, risks. Thus, the safe adoption of In Silico Trials should be at the core of the EMA strategy, and not only in connection with the reduction of animal experimentation.
In conclusion, we believe that it is important to recognize the huge potential that In Silico Trials have, not only in relation to animal alternatives, but also on the need to reduce the cost of innovation in healthcare. The adoption of In Silico evidences in the regulatory process poses a number of challenges, which need to be addressed at the strategic level. Thus, we recommend EMA to consider the inclusion in their strategic plan of a specific goal associated to the adoption of In Silico Trials."

Second choice (h)

9. Foster innovation in clinical trials

2nd choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

The term In Silico Trials indicates a number of use cases, not only related to pre-clinical evaluation, but also to the reduction, refinement, and in some cases even replacement of clinical trials (by in silico clinical trials). The VPH institute, together with the University of Sheffield coordinated a roadmapping project, Avicenna (FP7), where the challenges and benefits of in silico clinical trials were extensively discussed (http://avicenna-isct.org/wp-content/uploads/2016/01/AvicennaRoadmapPDF-27-01-16.pdf).

In in silico clinical trials, 'virtual' patients would be given a 'virtual' treatment, enabling us to observe through a computer simulation how the product performs and whether it produces the intended effect, without inducing adverse effects that might be potentially dangerous for the patient. We believe that such in silico clinical trial could help to reduce, refine, and partially replace real clinical trials by:

• Reducing the size and the duration of clinical trials through better design, for example, by identifying characteristics to determine which patients might be at greater risk of complications or providing earlier confirmation that the product is working as expected. In silico clinical trials might also be used to 'leverage' a smaller clinical trial population, by adding simulated patients that might fill gaps in the individual variability seen in 'real' patients. In silico clinical trials might also be able to determine those patients that will not respond to the candidate biomedical product. The removal of predicted nonresponding patients would potentially improve the outcomes of the clinical trials.

• Refining clinical trials through clearer, more detailed information on potential outcomes and greater explanatory power in interpreting any adverse effects that might emerge, as well as better understanding how the tested product interacts with the individual patient anatomy and physiology, and predicting longterm or rare effects that clinical trials are unlikely to reveal.

• Partially replacing clinical trials in those situations where in silico clinical trials can generate scientifically robust evidence. We already have examples where the regulators have accepted the replacement of animal models with in silico models under appropriate conditions. While real clinical trials will remain essential in most cases, there are specific situations where a reliable predictive model could conceivably replace a routine clinical assessment. During an event at the European Parliament on September 4th, 2018, the Irish based company Medtronic reported that using computer models for regulatory approval enabled them to release their new pacemaker 2 years earlier, allowing them to treat 10,000 patients and saving 10 Million Euro of testing cost (International Avicenna Alliance Report, avicenna-alliance.com/conference-2018 /conference-report-and-video/).

• Complementing clinical trials by offering the ability to test experimental scenarios, which would normally be less probable in real patient cohorts. For example: What if the patient has the disease under investigation, but also diabetes and a heart rhythm disorder?

• Augmenting clinical trials in cases where patient numbers are not or cannot be sufficiently large, such as rare diseases and pediatrics.

Third choice (h)

29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

3rd choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

There are a number of challenges for EMA associated with adoption of in Silico Trials, but a major one is that this “technologization” of the regulatory process requires different skills within EMA and among the advisory panels. As EU universities are starting only now to train specialists in In Silico Trials, it is reasonable to foresee a shortage of skilled workforce in this area in the next few years, which requires a strategic reflection.
Another challenge is that the FDA is clearly leading the way in relation to the use of In Silico Trials for the regulatory evaluation of medical devices, but, if we move quickly enough, there is an opportunity for the European Union to lead this revolution for the medicinal products and for Advanced therapy medicinal products. On the other hand, in the spirit of “collaborative competition” there is an urgent need for a harmonization effort between EMA, FDA, and other regulators around In Silico Trials.
Yet another challenge is that while there is a massive experience on the credibility assessment of predictive models in other industrial domains, In Silico Trials pose specific issues in terms of regulatory science. Dedicated research within the Horizon Europe program may be required, and EMA must play a central role in it.

Question 6 (human): Are there any significant elements missing in this strategy. Please elaborate which ones (h)

Some of the elements mentioned in the strategy could be extended beyond their described use in the strategy. As described above, the use of computer modeling and simulation should not only be restricted to the realisation of the 3Rs but should be an integral part of the regulatory toolbox at all stages of the process.

Question 7 (human): The following is to allow more detailed feedback on prioritisation, which will also help shape the future application of resources. Your further input is therefore highly appreciated. Please choose for each row the option which most closely reflects your opinion. For areas outside your interest or experience, please leave blank.

Should you wish to comment on any of the core recommendations (and their underlying actions) there is an option to do so.

Strategic goal 1: Catalysing the integration of science and technology in medicines development (h)

	Very important	Important	Moderately important	Less important	Not important

1. Support developments in precision medicine, biomarkers and ‘omics’	◉	○	○	○	○
2. Support translation of Advanced Therapy Medicinal Products cell, genes and tissue-based products into patient treatments	◉	○	○	○	○
3. Promote and invest in the Priority Medicines scheme (PRIME)	○	◉	○	○	○
4. Facilitate the implementation of novel manufacturing technologies	○	◉	○	○	○
5. Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	◉	○	○	○	○
6. Develop understanding of and regulatory response to nanotechnology and new materials’ utilisation in pharmaceuticals	○	◉	○	○	○
7. Diversify and integrate the provision of regulatory advice along the development continuum	○	◉	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation** you are commenting on:

Strategic goal 2: Driving collaborative evidence generation – improving the scientific quality of evaluations (h)

	Very important	Important	Moderately important	Less important	Not important
8. Leverage novel non-clinical models and 3Rs	◉	○	○	○	○
9. Foster innovation in clinical trials	◉	○	○	○	○
10. Develop the regulatory framework for emerging digital clinical data generation	◉	○	○	○	○

11. Expand benefit-risk assessment and communication	○	◉	○	○	○
12. Invest in special populations initiatives	○	◉	○	○	○
13. Optimise capabilities in modelling and simulation and extrapolation	◉	○	○	○	○
14. Exploit digital technology and artificial intelligence in decision-making	◉	○	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Strategic goal 3: Advancing patient-centred access to medicines in partnership with healthcare systems (h)

	Very important	Important	Moderately important	Less important	Not important
15. Contribute to HTAs' preparedness and downstream decision-making for innovative medicines	○	◉	○	○	○
16. Bridge from evaluation to access through collaboration with Payers	○	◉	○	○	○
17. Reinforce patient relevance in evidence generation	◉	○	○	○	○
18. Promote use of high-quality real world data (RWD) in decision-making	○	◉	○	○	○
19. Develop network competence and specialist collaborations to engage with big data	○	◉	○	○	○
20. Deliver real-time electronic Product Information (ePI)	○	◉	○	○	○
21. Promote the availability and uptake of biosimilars in healthcare systems	○	○	◉	○	○
22. Further develop external communications to promote trust and confidence in the EU regulatory system	○	◉	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Strategic goal 4: Addressing emerging health threats and availability/therapeutic challenges (h)

	Very important	Important	Moderately important	Less important	Not important
23. Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches	○	◉	○	○	○
24. Continue to support development of new antimicrobials and their alternatives	○	◉	○	○	○

25. Promote global cooperation to anticipate and address supply challenges	◉	○	○	○	○
26. Support innovative approaches to the development and post-authorisation monitoring of vaccines	○	◉	○	○	○
27. Support the development and implementation of a repurposing framework	○	◉	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Strategic goal 5: Enabling and leveraging research and innovation in regulatory science (h)

	Very important	Important	Moderately important	Less important	Not important
28. Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science	◉	○	○	○	○
29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions	◉	○	○	○	○
30. Identify and enable access to the best expertise across Europe and internationally	◉	○	○	○	○
31. Disseminate and share knowledge, expertise and innovation across the regulatory network and to its stakeholders	◉	○	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

By engaging with scientific communities, there will be a mutual beneficial effect. On the one hand, EMA can benefit from the expertise present within academia and, on the other, academics are becoming more aware of the regulatory reality and requirements. Through such common projects, EMA will gain expertise whilst academia can adopt (to a certain extent) a more rigorous attitude (in publications and projects) towards the development and dissemination of computer models of drug development. These include elements such as verification, validation, uncertainty quantification. Having such clear assessment frameworks (in EMA and academia) will allow to increase overall robustness and reproducibility of the digital evidence.

Thank you very much for completing the survey. We value your opinion and encourage you to inform others who you know would be interested.

Useful links

EMA website: Public consultation page (https://www.ema.europa.eu/en/regulatory-science-strategy-2025)

Background Documents

EMA Regulatory Science to 2025.pdf

Contact

RegulatoryScience2025@ema.europa.eu