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Public consultation on EMA Regulatory Science to 2025

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* Name

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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

* ***Please specify:***

between 1 and 1 choices

- [x] Individual company
- [ ] Trade association
- [ ] SME

Name of organisation (if applicable):

Pfizer

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 proposed EMA Regulatory Science strategy is very comprehensive and ambitious. Pfizer agrees with all the key priorities identified although we believe that not all activities are of equal importance and there needs to be prioritization. However, as the plan is inevitably high level there will be a need to comment further when detailed proposals are developed downstream and for the Agency to continue to fully involve Industry as a key stakeholder.

In addition, it would be useful to define some of the terms used in the strategy paper, for example by adding a glossary so that there is an aligned interpretation as some new generic terms appear to have been introduced which are not standard terms used and understood by industry, e.g. 'collaborative clinical trials', "healthcare actors"

Additionally, priority should be given to the goals/ activities which are realistic and can be led by the EMA compared to those which may be led by others. For example, by other national competent authorities and/or HMA. Some of the activities listed are already being led by others or co-led with the EMA (e.g. Electronic Labelling). Other advances such as in science and technology (e.g. ATMPs) will be followed by the EMA through normal working practices and therefore do not need additional focus, though do remain of high importance.

It would also be useful to specifically identify areas where EMA needs to collaborate with leading global regulators such as FDA as some of the items identified are ambitious topics where an internationally harmonized approach from the outset is very important, (e.g. Real World Data) On RWD we believe that while this is very important there are obstacles that are not within EMA's control such as harmonization of electronic health records and therefore it may be better to partner with FDA rather than assigning this as a top priority for EMA action.

One aspect which has not been considered in the paper is optimizing further the review time-lines and procedures so that medicines intended to treat unmet diseases benefit from radically reduced review times. For example, the FDA's oncology centre of excellence pilot on real time oncology review for supplements results in data being provided to the agency on a rolling basis from the time of the topline report and delivers greatly accelerated approval times. It is interesting to note that this is possible today with the current technology base and does not depend on further development in digital tools, although digital developments would undoubtedly help. EMA could consider similar pilot schemes.

https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

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)

9. Foster innovation in clinical trials

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.

Regulatory decision making, and systems are currently largely based on traditional clinical trial designs conducted in a sequential way. However, new innovative approaches to clinical trials employing adaptive designs, basket studies and using different evidence sources require new and flexible approaches from regulators to fully leverage the benefits. The current construct of CTA approval (using a 'per protocol' approach) does not lend itself to easily allow such designs to be implemented in practice. Novel approaches in science mean that protocols need to be amended, not because of poor initial design, but because the novel factor means that stakeholders are learning as they are doing and, thus there is a need to constantly adapt the approach. The current system for substantial amendments slows down clinical trials in the EU without providing benefits to patient safety as too many administrative amendments are categorized as "substantial". This puts Europe at a competitive disadvantage with other parts of the world and may serve to discourage companies placing more innovative multiregional clinical trials in European countries. Changing, or at least adapting, this paradigm therefore has the largest potential to fundamentally change the regulatory system and make it fit for the future. Failure to address this could mean that Europe becomes less attractive for clinical trials, especially as other countries are developing their clinical trial infrastructure, (e.g. China and S. Korea).

We believe that there is a need to fully explore the utility of real-world data and other evidence sources and the role they can play alongside more conventional clinical trials in bringing innovative approaches to clinical trials. We have considered RWD as a tool to serve within the innovation of clinical trials topic rather than a stand-alone topic. We also believe that RWD needs action from other players in order to enter mainstream use and that there are specific hurdles in Europe that are beyond EMA's remit to fix, (e.g. harmonization of electronic health records). Rather we believe that the competitive disadvantage Europe faces due to the inflexibility of the regulatory approval system for CTAs, is the most important area to focus on and therefore we have placed this topic as the number one priority.

Second choice (h)

7. Diversify and integrate the provision of regulatory advice along the development continuum

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.

Centralised scientific advice provided in the EU is considered of a high quality, appreciated by developers, and is generally fit for purpose. However, on occasions, industry would like to request a face to face meeting on complex issues which require dialogue, rather than only have meetings occur when regulators determine that there is a fundamental disagreement with the company's approach.

The overall value of pan-EU scientific advice is, however, undermined when contradictory opinions emerge during the development of a product. This can be through the different committees within the EMA (e.g. PDCO where it is a recognized problem) but also via the Member-State-led approach to decision-making for clinical trials. This national approach to clinical trials and EU centralized approach to the provision of scientific advice also means there is no unified "line of sight" on the progress of a product during its development from early clinical trials through to approval. This contrasts with the US IND system where the FDA has a holistic view. If a safety issue occurs for a product during development where clinical trials are ongoing and before a MAA has been granted the company liaises with individual national member states and ethics committees on actions to be taken but there is no centralized point of contact amongst EU regulators and there is no formal mechanism for dialogue with the SAWP and to keep them appraised of developments on a real time basis. Again, this is a disadvantage of the EU regulatory construct compared to other regions especially the US where the IND system provides an integrated view of development and clinical trials.

Innovative and flexible approaches need to be developed to enhance the scientific advice process to address these points and ensure that strong scientific input from EU regulators is provided and their voice is heard in designing global programmes. Developing and improving parallel advice with the FDA may also help to address this concern but does not solve the disconnect between EMA led scientific advice and national CTA approvals. A pilot could be used to better determine how to enhance support in a more holistic fashion for example by aiming for better linkage and dialogue between national CTA approvers and EMA - led scientific advice.

Third choice (h)

13. Optimise capabilities in modelling and simulation and extrapolation

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.

The topic of 'Optimising Capabilities in Modelling, Simulation and Extrapolation' is considered of high importance as currently regulators rely on 'actual data', often generated in real time, and are reluctant to accept alternative approaches to provision of evidence during development. Thus, increasing acceptance of predictive approaches, based on modelling, simulation and extrapolation will advance the clinical development of medicines and acceptance of models in the non-clinical and CMC / Quality fields will also add value. For example, predictive and modelled approaches to safety evaluation (for active substances, impurities and manufacturing intermediates) that minimise animal utilisation is a current field of interest that demands further investment and acceptance (see the recent EMA Reflection Paper on Qualification approaches for non-mutagenic impurities). In particular, the CMC / Quality arena is a rich field of scientific and innovative approaches using modelling, simulation and prediction that could be utilised, for example: -

o Stability modelling and prediction of degradation (for shelf-life setting and product and packaging selection) – changes critical path to development and post approval change
o PK modelling to support bioequivalence evaluation (beyond the BCS scope of ICH M9) and dissolution specification setting
o Process modelling (e.g. development of a digital twin) of a manufacturing process (drug substance and /or drug product) to support development and scale up and control strategy development. (This type of approach can be utilised for both batch and continuous manufacturing approaches and is thus also supportive of the introduction of innovative manufacturing technologies, which are also of considerable current interest – see the progress being made to develop harmonised guidance on Continuous Manufacturing under ICH Q13)
o Models built from prior knowledge that can support post-approval change (e.g. site transfer etc.) and the setting of clinically-relevant specifications (e.g. for biotechnological products within a platform family of products and processes)

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

An understated element in the strategy is the Innovative Medicines Initiative. IMI is a unique and powerful tool and yet is only briefly mentioned. A focus on how IMI should be leveraged by the EMA to deliver on regulatory science goals should be explicitly included particularly in Goal 1 and 3. It would be particularly helpful to add some goals on how some of the outputs from EMA could be leveraged going forward in informing future thinking/guidance development etc.

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:

Comments are made mainly on those recommendations of very high or very low priority to explain the rationale. For comments on the 3 highest priorities already identified, please see earlier responses.

Recommendation 1: Qualification of biomarkers is of high importance as the procedure and requirements for qualification need to be more practical and workable; the existing approach to qualification presents such high barriers to achieving success in a timely manner that it impedes the ability to rapidly develop innovative treatment. Industry should also be included in the collaboration to assess the impact of treatments on clinical outcomes measured by biomarkers. EMA could consider publishing a workplan to focus on specific biomarkers for high priority areas that industry can contribute to.

Recommendation 4: There needs to be a recognition that without effective and pragmatic implementation of initiatives in the pharmaceutical sciences and manufacturing areas efforts to capitalize on innovations in the clinical space to get innovative breakthroughs to patients faster will be compromised as manufacturing and CMC issues will become rate limiting. As part of its regulatory science strategy, EMA should place a focus on whether different approaches can be adopted to provide assurance of the quality of medicinal products. The concepts of modelling and simulation that have been developed to support efficacy and safety assessments could also be further developed and deployed to provide assurance of the quality of a medicinal product.

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**:

Recommendation 13: Modelling and simulation tools have the potential to radically streamline drug development. However, an efficient approach to the qualification of tools has not been fully developed meaning the potential has not been fully realized. In addition, experience has demonstrated that there is not a consistent regulatory acceptability of modelling and simulation approaches thus discouraging their adoption for modern drug development. As highlighted in our comments to Priority #3 above, less has been achieved in the development of manufacturing/CMC models, creating the potential for bottlenecks caused by CMC/quality issues.

Recommendation 14: The use of digital technology and artificial intelligence has the potential to transform the way we work in many different areas. Pharmaceutical development is lagging other industries in the exploitation of this technology. In the short term, the greatest potential is in safety reporting and monitoring, but longer term the application of digital technology has great potential. There is a skills gap within industry and the regulators and to capitalise on the opportunities presented, it will be important to build partnerships with technology experts and urgently build the necessary capacity and capability. Technical guidance and the development of specific qualification guidance should be developed as experience is gained. EMA could also be influential in developing ‘cloud submissions’ which move the focus from document-based point in time submissions to a continuous data-based approach.

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**:

Recommendation 15: It is widely recognized that regulatory approval of medicines is no longer the most significant hurdle to ensuring patient access to new medicines in Europe. HTA assessment and subsequent reimbursement discussions have become the key challenge facing the industry and the healthcare systems. If this continues, there is a danger that global companies will no longer choose Europe as a region for investment. Although this issue is not a regulatory issue per se, regulators do have a key role in collaborating with HTA bodies to ensure robust and scientific decision making and we believe that this is an area which EMA can positively influence with HTAs. A key area of focus should be standards of evidence that support regulatory decision making and thus the HT body standards with a view to aim for a harmonized standard of evidence between regulators and HTA bodies (EPAR could be expanded and used).

Recommendation 16: Though it is recognized that EMA collaboration with HTA is extremely important, collaboration with Payers organisations directly is more complex and the value should be carefully considered particularly in the context of multistakeholder forums. The criteria for decision making for payers is very different to the clinical assessment undertaken by the EMA and the complexity of the payer infrastructure across Europe means that EMA involvement may not be the most appropriate way to engage on this critical topic and could lead to complexity and delay in the regulatory system.

Recommendation 17: The patient voice needs to be incorporated into regulatory decision making in a more systematic and scientific way and with greater transparency of how patient preference information will be used in the benefit risk decision making. For example, it will be important that industry understands how patient preference is used by EMA committees in the context of benefit/ risk decision making, orphan maintenance opportunities etc.; i.e. is only statistical significance considered the hurdle or could it be acceptable to demonstrate only a positive trend on clinical outcome given that patient measures are subject to ceiling effects? In addition, patient input via PROs should be developed and focused upon, leading to more patient-centric labeling. Such an approach will also have an impact on enabling HTA evidence needs and decision making. Finally, it is important also that the EMA works closely with the FDA on this initiative to ensure a global approach. The output from the existing cluster group should be more transparent to industry.

Recommendation 21:We recognize the leading role which EU regulators have played in pioneering the “biosimilar concept”, the principles of which have been replicated and adopted by regulators around the world and by the WHO. However, we do not consider that promotion of the availability and uptake of Biosimilars in healthcare systems to be a regulatory science topic. As a Biosimilars developer that also develops novel biologics, we do not foresee any significant innovations that would change the way in which Biosimilars need to be developed. We consider that comparative clinical data in the most sensitive population will still be needed to resolve residual uncertainty and ensure that there are no clinically meaningful differences. Mechanisms to promote the uptake and availability of Biosimilars are not regulatory issues that are within EMA’s remit and are determined by national member states. For these reasons we have scored this as a low priority.

Recommendation 22: Overall, we believe that trust in the regulatory framework is good and therefore this is of low priority for additional initiatives. However, this may be of higher priority and focus for some specific sectors for example vaccines, where there are some erroneous perceptions which could be addressed to some degree by building the public’s knowledge, understanding and trust in the regulatory decision-making process.

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**:

Recommendation 24: Development of new Antimicrobials is a very high priority for Pfizer. However, the most significant challenges in this area related to the business model and incentives. Innovation in the regulatory and clinical requirements are part of this but are already under development and already have a high focus at the EMA.

Recommendation 25: The paper acknowledges the complexity associated with the broad causes of shortages (which go beyond purely the manufacturing aspects). It will be important to be able to develop solutions based on the messages given at e.g. the FDA Public meeting last November.
Recommendation 27: In the existing framework, where an unmet need is identified, and data and a scientific case is available to support the development of an existing product for a new indication it is already possible to do so. It is therefore unclear what additionally needs to be addressed.

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**:

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