Public consultation on EMA Regulatory Science to 2025

Fields marked with * are mandatory.

* Name

* Email

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):

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.

This response is delivered by the Future Targeted Healthcare Manufacturing Hub based at University College London (UCL). The Hub has 5 academic spokes at leading UK universities and is partnered with 39 external companies and organisations. The Hub is addressing the manufacturing, business and regulatory challenges to ensure that new targeted biological medicines can be developed quickly and manufactured at a cost affordable to society. A copy of the Hub 2018 annual report can be found at: https://www.ucl.ac.uk/biochemical-engineering/sites/biochemical-engineering/files/fthm-hub-annual-report-2018.pdf

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We endorse EMA's commitment to develop a strategy to keep pace with scientific, technological and informational innovations. We welcome and support the clear statement (p. 5) that the interests of patients and their carers are at the core of the network's mission.

We welcome that the EMA acknowledges the importance of promoting innovation and facilitating the development and adoption of beneficial and sustainable innovative medicinal products (p.2 [Vision - Human medicines] and p. 5). We also encourage the EMA to continue to enable the development of innovative products that are supported by robust evidence that demonstrates improved quality, safety and therapeutic value. We recommend that the EMA specifies more consistently this requirement in its recommendations. For instance, the box on p. 8, states explicitly that innovation needs to meet safety, quality and clinical appropriateness criteria, while section 3.1.2 emphasise support for clinical translation of ATMPs without mentioning explicitly that they need to establish their safety, quality and clinical value.

We praise the commitment to developing regulatory science so as to ensure that new medical technologies are assessed on the basis of appropriate and robust science and methods. However, we believe that these new methods need to be developed through an effort that involves all relevant stakeholders, so as to ensure consensus on their robustness and acceptance. Such an engagement will also help to make more explicit and understandable the basis of regulatory decisions and reduce uncertainties for product developers.

In areas like ATMPs, developers may struggle to have a clear picture of the requirements they will have to satisfy at different development stages. On various occasions we have noticed that clinical and manufacturing requirements are not easily anticipated by developers. In particular, greater clarity on CMC expectations for submission versus post-marketing commitments would help innovators pursuing expedited pathways for innovative therapies.

While the 'Regulatory Science to 2025' strategy' document is mainly addressed to stakeholders, we believe that in the interests of transparency and accountability , the EMA should strive to make its strategy documents as clear and readable as possible. This can be achieved by removing excessive technical language and jargon. Public trust in the operation of the Agency is dependent on the ability of the public to understand its initiatives and what they imply in practice. Therefore, we strongly encourage the EMA to explain in greater detail the practical implications of the proposed goals and actions.

In particular, we feel that for each goal, the Agency should make explicit what are the specific problems/challenges that it aims to address. In addition, in order to avoid unrealistic goals or timelines the EMA should try to estimate the resources, capacities, and time required by the proposed actions, as well as considering whether it has the needed legal mandate and powers to achieve them.

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

Comments on strategic goal 1 (h):

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

We do consider this goal appropriate. However, we would like to make some comments.

The EMA needs to keep pace with the latest scientific and technological knowledge. We believe it is important to note that its core duty should be to ensure that innovations and assessment methods are mature enough to deliver products and tests that meet the standard of evidence and epistemological robustness applied to more established technologies.

We support the EMA engaging with academia and industrial developers to anticipate which innovations are in the pipeline and then collaborate with independent scientists, engineers, clinicians and patients to develop the appropriate methods and knowledge to assess adequately new medicinal technologies and products.

We believe that the PRIME scheme deserves to be promoted. However, we suggest that the EMA pays attention to some obstacles that poorly resourced developers (academia, hospitals, small biotech companies) may have in joining a resource intensive scheme that may interfere to their achievement of milestones needed to secure further funding or capital. Agency advice and guidance seem to work well for those developers that have enough resources (capital, staff and in-house expertise). On the other hand, this could be potentially intimidating for less resourced developers that may not be able –or cannot afford– to fully comply with the EMA's advice, or that do not aim to develop the product all the way to commercialisation.

To address this problem, we suggest that a system of grants for academia and SMEs developing Advanced Therapy Medicinal Products (ATMPs) may be extremely helpful and is a possibility worth exploring. Similarly, the Certification process could be extended to certify that further stages of development (including aspects pertaining to CMC development) have been performed in compliance with the Agency's requirement. The suggested mechanisms could encourage developers who are not planning on bringing the product to the market themselves to follow a more rational development plan and to raise funding/capital (this proposal seems to us consonant with the suggestions put forward by Fergal Donnelly in the Journal of Regulatory Science [issue 4, 2016, pp. 21-8]).

We strongly support the intention to facilitate the implementation of new manufacturing technologies (3.1.4). We believe that a commitment to the success of ATMPs cannot work without attention to manufacturing and controls. We therefore strongly encourage the Agency to promptly provide regulatory clarity and guidance in order to facilitate the adoption of manufacturing processes, technologies and logistics that will improve the quality, safety and consistency of the final products, as well as reduce waste, risks and manufacturing times.

We were pleased to read EMAs strategic plans for nanotechnology and their application toward the development of pharmaceuticals and medical devices.

We feel it is important to note that nanomaterials are being developed to improve analytical processes and enhance the manufacture of cell and gene therapies (Augmenting automated analytics using fluorescent nanosensors VM Chauhan, Cell & Gene Therapy Insights 4 (9), 837-850 & Enhancing cell and gene therapy manufacture through the application of advanced fluorescent optical sensors RP Harrison, VM Chauhan Biointerphases 13 (1), 01A301).

Where these novel systems are transferred to final products for patient treatment, the implications of their biodistribution and biological effects should be considered for regulatory guidance. We would encourage the Agency's early action to produce regulatory guidelines for innovative nanomaterials that enhance pharmaceutical production. We anticipate that this will overcome challenges for their early adoption, which in the medium- to long-term could accelerate medicinal products' development and improvement.

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

○ Yes
◉ No

Comments on strategic goal 2 (h):

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

This Strategic goal to drive collaborative evidence generation lacks specificity and covers a very broad variety of possible actions. A number of these actions could be considered more urgent and realistic than others, as we explain below.

We suggest that the problems that this strategic goal attempts to address are disaggregated. Digital technologies operating at different stages of the medicinal products lifecycle (manufacturing, optimisation, clinical trials, clinical use and patients experience) generate very different technical, legal, social and ethical challenges. For instance, the challenges associated with digital technologies that are applied to monitor bioprocessing are different from the challenges associated with data generated by using wearables for trial recruitment or to determine patients' eligibility for treatment. Therefore, we believe it is important that priorities are set clearly and a realistic appraisal are performed regarding the timeline for developing standards for different types of technologies and data interpretations.

We also believe it is crucial to improve the transparency of benefit-risk assessment, especially to the stakeholders involved in therapeutic choices (providers, payers, clinicians, patients). We do not believe that the lack of alignment between regulatory agencies and other stakeholders such as Health Technology Assessment (HTA) bodies and Payers on the benefit-risk assessment can be solved with better communication from regulatory agencies.

While intensifying communication and agreeing on the scientific aspects are surely desirable goals, they will not change the fact that regulatory agencies and HTA bodies and Payers have different missions and constraints. This is because these stakeholders in their decisions consider different types of risks, which include impact on the budget, healthcare system, distribution of resources and the allocation of staff. Furthermore, in Europe HTA bodies and payers operate at national level and respond to national policy decisions. Therefore, while collaboration and agreement around evidentiary standards is desirable, it is not sufficient to achieve alignment. Considerations like these should lead the agency to reconsider how realistic is its ambition to expedite access to innovative therapies, and what trade-offs are justified by pursuing a goal not fully under its control.

We agree that in pre-clinical development and testing, modelling and simulation are surely going to be very important and potentially valuable tools. However, the resources required to demonstrate scientific robustness and confidence in the models should not be underestimated. Winning the trust of the public is also necessary and may require in-depth involvement of different stakeholders. We suggest that the EMA collaborates with other interested agencies, such as the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA).

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

○ Yes
◉ No

Comments on strategic goal 3 (h):
Please note you will be asked to comment on the core recommendations and underlying actions in the subsequent questions.

Using the expression "patient-centred access" without further definition may be confusing to some readers. The expression patient-centred medicine (sometimes person-centred medicine or healthcare) has come to identify a more holistic approach to medicine that considers central the experience of the person, their needs and their active and informed involvement into their therapeutic decisions. Only a few points in goal 3 appear to align with this framework: most notably the focus on patient reported outcomes (PROs) and on the development of tools to assess quality of life (QoL) in clinical trials. Therefore, labelling this goal around patient-centredness may be misleading.

This goal should rather be formulated in terms of addressing the many challenges in developing methods, infrastructures, capacities and financial resources for producing real-world evidence (RWE) –not just real world data– of robust scientific quality for product lifecycle evaluation. This is a very pressing need that should have high priority, since several new regulatory pathways emphasise the importance of lifecycle evaluation of medicinal products rather than the traditional focus on the evidence produced before marketing authorisation. However, the mechanisms to ensure its timely and effective performance are yet to operate as successfully as required. This is pointed out, for instance, by the criticisms and perplexities voiced by the German Institute for Quality and Efficiency in Healthcare [IQWiG] and researchers from the Mario Negri Institute. The limits to existing methods and practices in post-marketing data gathering have also been acknowledged by the EMA itself, for instance in its final report on Adaptive Pathways (for a recent interesting discussion of some similar challenges in the USA, see volume 15 (3), 2018 of the journal Clinical Trials).

A recent publication by Calvert and colleagues in Nature Drug Discovery shows how much work is still needed in order to improve the quality, consistency, harmonisation and usability of Patient Reported Outcomes (PROs). We believe that the agency's and network's effort should focus on the essential task of improving the quality and the timely collection of post-marketing data, RWE and of PROs.

Some of the other recommendations and questions (e.g. 3.3.1, 3.3.2, 3.3.5, 3.3.6 and 3.3.7) do not seem to address the same concern and should be placed under another heading.

Some challenges are of great importance, in particular the co-ordination with payers and HTA bodies, since no timely access can be achieved without their endorsing the belief in the efficacy, value and affordability of innovative products. However, we believe that the challenges and obstacles that prevent a better coordination with HTA bodies and payers are underestimated in the way some recommendations and actions are formulated. In the context of the principle of subsidiarity between the EU and member states, it cannot be ignored that HTA bodies work at national levels and respond to national policies. The EMA should not set for itself too ambitious goals that are unrealistic within current legal and political frameworks.

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)

4. Facilitate the implementation of novel manufacturing technologies

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.

Novel manufacturing technologies are required to enable feasible business models and sustainable supply of innovative therapies such as patient-specific ATMPs like autologous CAR-T cells. However, this can only be implemented with more research in strategic areas of regulatory science. Here we see the following goals as especially pressing:

•   develop regulatory guidance (both in terms of guidelines and in terms of timely scientific advice) on the CMC development pathways and commitments required to satisfy regulatory requirements;

•   actively support innovation and standards in analytical, metrological and diagnostic technologies to aid the more effective development of products, the targeting of patient populations and the quality of manufactured products;

•   promptly provide Agency's guidance around the regulatory requirements for automated, closed systems for manufacturing advanced biological therapies, especially in case of their use at the bedside, where responsibilities and applicable standards may become unclear.

Second choice (h)

15. Contribute to HTAs' preparedness and downstream decision-making for innovative medicines

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.

Cost-effectiveness of emerging cell and gene therapies is based on evidence from clinical effectiveness studies, preferences regarding health outcomes and the cost of technologies. Uncertainty in the available evidence affects the estimates of incremental costs, health benefits and the decisions made about implementation of these therapies. Potential solutions to addressing uncertainty have been managed entry agreements (MEAs), which ensure the risks and benefits of technologies are shared between the payers and manufacturers. In addition to MEAs, we recommend the introduction of EU clinical registries post-launch, with input from the EMA and HTA bodies on data requirements. Clinical registries would provide highly structured clinical data to healthcare professionals on safety and effectiveness, and can be used to compare the effectiveness of different treatments for the same disease or condition. However, we recognise that registries would require significant investment in registry design, operating data systems, training and licencing. The cost of running the registries should be factored in HTA evaluations, with further discussions on the distribution of costs between the payer and manufacturers.

A distinct feature of clinical trials for cell and gene therapies are that they have tended to be small, single-arm, or single-centre, early phase clinical trials. In the context of Europe's publicly funded healthcare systems, it is evident that they are not geared to make one-off, large up-front payments for therapies with uncertainty. Amortisation and payment by performance models have emerged as a means to financing high-cost technologies. We suggest, HTA bodies stipulate a resource impact assessment applying the annuity and payment by performance models. This criterion would serve as a tool to predict future expenditure and identify the best reimbursement model early on.

Finally, we expect the HTA bodies to authorise more cell and gene therapies with conditional approval in the future. It is important to understand how the HTA bodies plan on addressing the commissioning and decommissioning of future therapies. We suggest, the EMA and HTA bodies evaluate the safety and efficacy of the therapies in consultation with one another, to create a culture where they work in parallel to meet their objectives. This will avoid duplication of data review and expedite the pathway to the clinical adoption of safe and effective products and to the discontinuation of products not performing.

Third choice (h)

28. Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science

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.

Collaboration with academic research centres, such as the Future Targeted Healthcare Manufacturing Hub, is necessary and desirable. Mutually beneficial opportunities like this will permit exchange of scientific insights, whilst providing a platform to assess its next generation ideas and tools with its large industrial consortium. Mechanisms that facilitate access to EMA experts to discuss regulatory science questions around emerging paradigms will be critical to enabling their success. This may help in creating a better knowledge flow that can support a more effective and timely development of regulatory science.

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

We suggest that the challenge of developing more timely and robust post-marketing evidence that is trusted by all stakeholders is an objective to which a strategic goals could usefully be dedicated. While some of the scientific aspects have relevant similarities with other objectives, the context in which this evidence needs to be collected, stored, curated, assessed, validated, communicated and accepted is considerably different from the context in which pre-marketing evidence is produced and used. This would justify a dedicated strategic goal.

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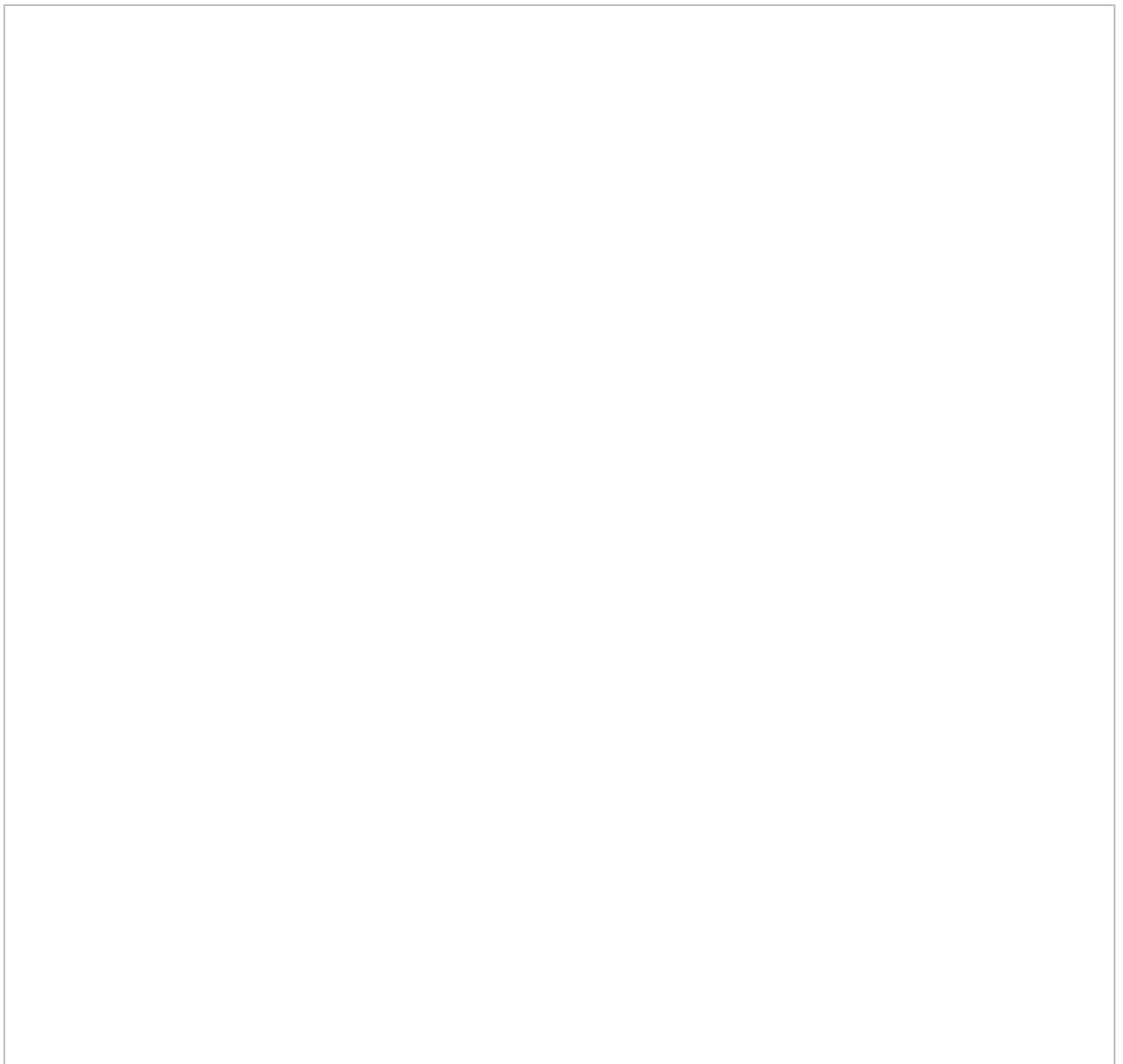
Thank you very much for completing the survey. We value your opinion and encourage you to inform others who you know would be interested.

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

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