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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):

European Organisation for Rare Diseases (Eurordis)

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 addresses important issues rightly, e.g. the integration of science and technology in medicines development or advancing patient-centred access to medicines.
With this strategy, EURORDIS hopes the rare disease community can move from "The greater the complexity in drug development, the greater the failure risk", to "the greater the complexity, the more the guidance and the efforts, and the lesser the failure".
Facing the increasing complexity of the regulatory science and of the scientific challenges, there is a risk that society, and patients in particular, lose track of the methodological changes driving the development and the evaluation of medicines. This is the case with movements representing vaccine-sceptical citizens, but not only. A public debate exists on the quality and relevance of EMA's work, e.g. recent criticism of recently authorised treatments in oncology which therapeutic benefits are not immediately clear. This debate is useful, and this strategy is a contribution to providing answers.
Progresses in regulatory science can certainly contribute to lower the risk that ineffective or not-so-safe products are authorised to be used in humans. They can also contribute to reducing the risk that yet effective ones are rejected.
While the public debate focuses on the former, i.e. the authorised products put into question, there is no equivalent debate on the latter, the rejected or withdrawn products. And yet, some fail due to poor quality development, failure to request or adhere to scientific advice, inappropriate scientific choices.
Associating the public in all its activities is probably the most effective strategy to ensure avoid this disconnect, and the engagement of citizens in EMA's activities can only increase. The public hearings organised by the Committee for Pharmacovigilance and Risk Assessment are one successful approach and other scientific committees could certainly gain from this experience.
Orphan medicinal products and other products for rare diseases are concerned by these debates. Rare diseases are the world of unmet medical needs, methodological and practical difficulties, rare and scattered expertise, ethical challenges but also of huge investments. While the EU Regulation on Orphan Medicinal Products has certainly initiated the process of creating a more favourable scientific and economic environment for these products, time has come to reflect from the experience of the orphan designations and subsequent authorisations since 2000. Regulatory challenges exist that explain some of the difficulties (e.g. access to clinical trial data for the repurposing of products, e.g. classical clinical trial designs that do not fit with small populations), and on the other hand major opportunities open new perspectives: closer regulatory guidance (PRIME), better understanding of biomarkers and "omics", novel non-clinical models, new designs, artificial intelligence, synergies between regulators, HTA and payers…
Even if all opportunities taken into consideration by the Regulatory Science Strategy 2025 seem relevant and well thought, EURORDIS would like to highlight some which might seem overlooked.

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)

3. Promote and invest in the Priority Medicines scheme (PRIME)

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.

Regulating the development and the evaluation of medicines means more guiding the developer than policing these activities. PRIME main characteristics that explain EURORDIS's interest are:

- Focus on unmet needs: even in the absence of a consensus definition of the term "unmet medical need", there is no dispute that all products selected to benefit from the PRIME scheme represent a public health need, for severe diseases or severe disease stages where too few treatment options exist
- Iterative scientific advice: Scientific advice helps minimising risks, it increases chances that adequate data are submitted to regulatory authorities when evaluating the benefit/risks. With iterative scientific advice, the developer can be adapted the development to the evolution of medical science
- PRIME reduces the risk that effective products are rejected due to wrong made choices by the developer
- Possibilities of a multi-stakeholder process, where patients, clinicians, health technology assessment experts can join the discussions

Needs to be improved: PRIME starts with a kick-off meeting where regulators take the time to familiarise with the product and its development plan. Patients and clinicians are not invited to these discussions, and yet they should be. It could also be interesting to invite some representatives of payers in PRIME discussions.

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.

Innovation in clinical trials is needed for several reasons:

- Randomised clinical trials RCT, considered as the gold standard, can be improved with the use of big data analysis (e.g. using virtual placebo comparator arm, virtual trials where the patient uses connected devices that inform on the efficacy from a distance with patient reported outcomes measures)
- RCT can be challenged when the effect size is expected to be high and there is no other comparator than placebo, in situations where standard of care is not satisfying. Patients do not accept to be randomised to a placebo, as the equipoise is no longer respected to their opinion. Instead, open label trials are proposed, with a treatment effect so large compared to historical data that the results can only be attributed to the product efficacy and not to a confounder. Other methods are then needed to determine the toxicity profile.
- RCT are difficult to organise in small populations, when large numbers of patients are needed. Since its guidelines on Clinical Trials on Small Populations published in 2005, some progress were made by the industry to experiment different treatment designs (e.g. adaptive trials) but with limited experience so far. IRDIRC, the International Rare Disease Research Consortium addressed clinical trials in small populations (https://rdcu.be/bHHhY), as well as three European projects (Asterix, Inspire and Ideal), as presented at the EMA workshop on trials in small population in 2017. Here again, how to transfer the outcomes to clinical trial centres in the whole of the EU is a key element for their developments.
- Shortly thereafter, the EMA updated a guidance on confirmatory clinical trials with adaptive (or flexible) designs (2007)
- In their review of the first 59 scientific advice letters for adaptive trial designs, the authors have shown 4 products that benefited from such a trial were submitted to the EMA for evaluation of the benefit/risks. This is a start, and the EMA needs to foster these activities (Adaptive designs in clinical trials: from scientific advice to marketing authorisation to the European Medicine Agency. Olivier Collignon et al. Trials. 2018; 19: 642.)

Needs to be considered: new design does not mean lowering the regulatory standards for clinical research and/or evaluation. The quality requirements and the level of regulatory demand need to remain high. 59 such letters covering 2007-2012 is a signal that something has been initiated, but not on a large enough scale.

Third choice (h)

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

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.

EURORDIS realises and deplores that too often authorised medicines are not available to patients as they should be. There are cases where the price is probably abnormally high for the member state's health budget, but in other cases, the clinical benefit is too modest for the proposed price or the quality of the evidence is too weak to convince payers to cover/reimburse the product.

- A dialogue between regulators and heath technology assessors exists (parallel EMA/HTA scientific advice) and needs to be strengthened to reduce the risk that inadequate information is provided to EMA and /or HTA at the time of evaluation.
- Exchange of information can take place for the assessment of the product by HTA bodies in the frame of EUnetHTA permitting HTA assessors to receive scientific information in parallel to the CHMP evaluation.
- Both the EMA and HTA bodies agree on the necessary cooperation, cf The HTA Network Reflection Paper on "Synergies between Regulatory and HTA Issues on Pharmaceuticals" to which EURORDIS participated (https://ec.europa.eu/health/sites/health/files/technology_assessment/docs /ev_20161110_co06_en.pdf)

However: some regulatory concepts do not fit easily in HTA approaches, such as surrogate endpoints (when the relation between the endpoint and clinical ones has not been completely established), or conditional approval. Other times regulators and HTA experts may have different views on the population to benefit, or the significant benefit for orphan medicinal products. This can result in lengthy HTA processes and/or a negative reimbursement decision, or in important restrictions on the population eligible for reimbursement /coverage.

Important efforts are needed to ensure cooperation between EMA and HTA bodies includes post-authorisation studies that can confirm the benefits in real world settings and better appreciate the safety profile: post authorisation safety and efficacy studies, registries and observational studies. These studies are not often defined jointly by regulators ad HTA experts (with the exception of newly introduced PLEG "Post-launch Evidence Generation" by EUnetHTA with little experience so far).

It could be useful to invite HTA experts to CHMP discussions for issues that are known to be a cause of difficulties for the downstream decision-making. The same applies to technical guidelines, where EMA and HTA bodies develop different sets of guidelines on the same topics, which can result in counter-productive divergences.

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

EURORDIS appreciates the innovative aspects of the regulatory science that are part of this strategy, yet this should not be to the detriment of current regulatory methods which can still be improved in some domains that are sometimes overlooked. To be prepared for what is coming is one thing, to amend and improve what already exists but has not delivered its best is another one.

a. Compassionate use programmes as a source of real world evidence prior to the marketing authorisation represent an important potential. The EMA has a limited mandate and in its Communication on Rare Diseases in 2008, the European Commission proposed the EMA to review its guidelines on compassionate use programmes with the objective of ensuring "A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs".

In its position on compassionate use (April 2017), EURORDIS made series of proposals to the EMA to enlarge its role on the anticipation of compassionate use programmes (http://download2.eurordis.org.s3.amazonaws.com/positionpapers/Compassionate%20Use%20Position%20Paper.pdf)

b. Evaluation guidelines are another example where the EMA could have an important impact. For the moment, they are developed once a first product is evaluated for a given disease.

However, when a second product starts development, the guidelines might already be outdated. And for diseases where no one has ever developed a product, there is no regulatory guidance.

The development and/or update of guidelines for all diseases would be an impossible task, if initiated by the EMA. But based on recent initiatives (EU Regulatory Workshop – Ophthalmology in 2012, scientific workshops for Duchenne Muscular Dystrophy, workshop on Spinal Muscular Atrophy…). In these multi-stakeholder meetings, the focus was set on clinical development and methodological issues, including the choice of outcome measures that are relevant to patients, evolving towards a common understanding among regulators, academia and industry…

For rare diseases, we propose the reflection on guidelines could be initiated by patients, clinicians, academic researchers and different industries as part of the activities of the European Reference Networks (ERNs), among other possibilities. When the reflection reaches a mature stage, a draft guideline is then proposed to the EMA which can decide the organisation of a scientific workshop, or initiate a process to validate the guidelines with its scientific committees.

Reflection should include inter alias the disease natural history and knowledge gaps, the relevance of a disease register, relevant clinical outcome measures or surrogate endpoints, possible patient reported outcomes, and this document should be made public to benefit all potential developers to lower risks when investing in R&D for this disease.

c. Pro-active role of patients to influence the development at an early stage

There are situations where patients would like to influence the development of a compound even before clinical trials in human start. Patients' representatives can have discussions among themselves or with pharmacologists and other experts. When patients have concerns, how can they effectively share them with regulators?

d. In house Research budget: Regulatory Science Research: taking stock of the participation of EMA in projects such as IMI PROTECT, and given the need for more research, the absence of a research budget at the EMA can be a limiting factor. With the exception of some pharmacovigilance studies initiated and funded by EMA, the EMA can hardly mandate members of the Academic network to conduct research in domains where the EMA would need to learn more. Unlike the FDA that can offer research fellowships or directly fund research, the EMA does not have this facility

e. Economic information: the EMA has no competence on the pricing of pharmaceuticals, yet it has some competences on economic valuation. This is the case for orphan products, where the COMP can grant orphan drug designation based on an economic criterion (and not just on a prevalence one), this can also be the case to implement article 8.2 of Regulation 141/2000 on orphan products when the product is sufficiently profitable not to justify maintenance of market exclusivity. It would certainly help to develop this expertise, for example by partnering with health economic universities to acquire more competence in this field.

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**:

all
An important aspect for the development of medicines is the conduct of high quality clinical trials. By participating to clinical trials, clinical centres acquire expertise and excellence, and learn how to use the product. This is particularly important for medicines requiring complex procedures.
Yet, the expertise to conduct high quality trials is not well distributed in the EU. In MS which joined the EU more recently, patients are struggling to joint clinical trials. This is sometimes also the case in the so called EU15.
Therefore, EURORDIS proposes to add:
- Support the organisation of high quality clinical trials by participating in the training of clinical investigators and facilitating the transfer of knowledge to MS with fewer experience in conducting clinical research for regulatory purposes, as "applied regulatory science" programme. To this aim, the EU Network Training Centre for capacity building could certainly play an important role, as well as European Reference Networks.

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 16:

As highlighed in Eurordis's comments to this consultation, the importance of involving payers representatives in the regulatory framework is key to bridge from evaluation to access. This recommendation is the 4th top recommendation Eurordis would mention.

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

RegulatoryScience2025@ema.europa.eu