Public consultation on EMA Regulatory Science to 2025

> Fields marked with * are mandatory.

* Name

* Email

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):

Association of European Cancer Leagues (ECL)

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.

Every new strategy should be based on a comprehensive risk-benefit assessment which would identify what needs to be changed, improved or what works well in existing context - especially as the current regulatory scheme has been in place for a number of years. The Association of European Cancer Leagues (ECL) lacks this 'lesson learned' approach in the new regulatory strategy.

The focus of the strategy should be on the ultimate goal of enabling equal access to high quality medicines European patients. The EMA should ensure that medicines coming to the EU market demonstrate sufficient evidence on their safety, quality and efficacy. In that fashion, regulatory requirements (data provided by manufacturers) should be adapted, so they meet the demands of HTA bodies, payers, patients and the society. The EMA should properly address shortcomings of approved drug efficacy reported in several studies, including the 'Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13' from BMJ, 2017.

Engagement with patients shall be consistently addressed throughout the document (not only in relation to data collection). It is also necessary to include a strategy on safeguarding transparent relationships with stakeholders and guarantee strong conflicts of interest (CoE) measures are in place.

Transparency should be the key principle in this document, not only when it comes to CoE, but also in terms of availability of information provided during scientific advice, committee meetings (including reasoning for decisions) etc. Data of clinical studies results should also be public.

Overall, ECL finds the strategy is comprehensive, yet very general, without specific indications where an update of legislation or guidelines/measures is appropriate. Furthermore, necessary follow up with national authorities should be an integrated part of this strategy, to prevent discrepancies in implementation of legislation (e.g., Directive 2001/83/EC) and to ensure EMA's decisions are properly implemented in EU MS. The strategy misses this "local" dimension - necessary if EU regulatory scheme is to work properly.

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.

The EMA should endorse a patient-centric approach as opposed to a drug-centric approach.

It is important to strengthen the scientific requirements and relevance of RCTs used in the marketing authorisation process. RCTs (particularly Phase III) should collect patient data in relevant subpopulations which will be treated in the clinical practice. Gender and age differences and other relevant subgroups must be reflected in RCTs.

Data from studies used for authorisation should be available for re-analysis as is the case with the U.S. Food and Drugs Administration (FDA).

EMA should consider the duration of the treatment in the assessment process.

In order to improve trust in the EU regulatory system, it could be envisaged to:
a) demand comparative RCTs where possible;
b) require that one of the 2 RCTs for approval be done by an independent party
c) pool resources across Member States to do meaningful-pragmatic RCTs responding to the right questions of clinical practice;
d) require superiority trial whenever possible rather than non-inferiority trial;
e) studies should be done to validate surrogate endpoints. Moreover, the use of surrogate endpoints should be discouraged nor accepted where final outcomes are achievable within a reasonable timeframe;
f) demand independent data analysis and trial pre-registration (registered report) and independent input into the trial design (or at least the ability to comment – e.g. expanded transparent scientific advice).

In terms of the post-marketing authorisation generation of evidence (about the efficacy and safety of new medicinal products) emphasis should be paid to the reporting of adverse effects. Similarly, real world data (RWD) shall be systematically collected and, where possible, used in the regulatory decision-making. E.g., while RWD can be used to characterise the patient population in clinical practice or to collect data on resource use it is challenging, yet necessary, to generate robust RWD on treatment side effects.

The regulator should view RWD as supportive evidence or signal eliciting evidence but should be cautious using this data to establish clinical effectiveness due to high confounding. Furthermore, there needs to be a distinction between real world data (RWD) and real world evidence (RWE). RWE should include pragmatic trials as in "close to everyday practice". "Close to everyday practice" is independent of the study design, it can be done in uncontrolled (single arm) and controlled (both non-randomised or RCTs) trials.

In addition, appropriate quality criteria should be defined before any use of RWE (indicatively: who assesses the data, what is high-quality and to whom, is the appropriate infrastructure in place to collect and assess this sort of data, what are the checks and balances to protect against bias).

Second choice (h)

11. Expand benefit-risk assessment and communication

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 push for accelerated approvals and the proliferation of conditional approvals must be evaluated against the original purpose of these flexibilities. They need to remain the exception as they increase uncertainty and put patient safety at risk. Hence, patients need to be fully aware of the benefit-risk ratio of these products. This must be clearly and sufficiently communicated to them (as well as to healthcare professionals).

The agency should ensure that submitted data answers clinically relevant questions rather than just demonstrates safety. Regulatory decisions should be guided by clearly defined, unmet public health needs.

Pharmacovigilance activities should remain a priority for the Agency .

Third choice (h)

22. Further develop external communications to promote trust and confidence in the EU regulatory system

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.

It is of utmost importance to maintain European citizens' faith in the work of the EMA. The Agency needs to welcome and endorse constructive criticism and foster a dialogue with critical voices. Most importantly, it needs to proactively dispel any mistrust caused by the links with the pharmaceutical industry. The EMA is a regulator defending the public interest and promoting public health. In terms of the relationship with drug developers, the Agency must show they care for patients by demanding developers to bring sufficient and relevant evidence, also in post-authorisation stage.

The perception of the Agency's independence and integrity is equally important. Therefore, it is the Agency's responsibility to proactively dispel any fears about regulatory capture.

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

- A critical review of existing legislation and practices in order to identify necessary changes to the EMA strategy.

- A critical review of the implementation of the orphan drugs legislation is important to ensure that the incentives foreseen by the legislator are not abused, misused or overused to the detriment of patients.

- More emphasis should be given to added value of new treatments over existing alternatives. Reasoning for regulatory approval should be clear and transparent.

- Pharmacovigilance is practically never mentioned in the strategic document, while it is a key role of the EMA. The Agency should first and foremost guarantee that the medicines on the market are safe, and the activities of pharmacovigilance should be strengthened with drugs arriving on the market at an early development stage. This is particularly important in accelerated approval schemes and CMA.

- EMA should enforce stricter criteria in post-marketing authorisation trials and surveillance. This includes appropriate study designs and endpoints to close remaining information gaps at the point of marketing authorisation. Chapter on new data evaluation should be added.

- The strategy of the EMA should include a reflection on the increasing risks of conflicts of interest raised by the planned strategy, which proposes to increase tremendously scientific advice and early relations with drug developers, with the risk to transform the EMA in a co-developer of medicines. The set up of an ethics committee with external and independent personalities should be planned.

- Local regulatory practice should also be analyzed as EU regulatory system based on Directive 2001/83 and Regulation 726/2004 encompasses both centralized regulatory bodies (in part. EMA and EU Commission) and local ones (local regulatory agencies).

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:

In goal 1 ECL appreciates:
- Increased collaboration with HTA, notified bodies (devices), payers and patients
- Focus on increased assistance in areas of unmet need
- Attention given to post-approval evidence generation and monitoring (in addition, this should be followed by re-evaluation where appropriate)

ECL calls for:
- More focus should be made not on (accelerated) innovation and new products, but on their efficacy and evidence-based benefit they bring to patients. (all of goal 1)

- Patient safety and pharmacovigilance should be considered strongly in this goal. (all of goal 1)

- Affordability and access to ATMPs should be elaborated on more strongly (though calling for 'creative' payment models is a vague statement, outside of the mandate of the EMA) (goal 1.2)

- Claim that the PRIME scheme 'has been broadly successful' shall be supported by evidence. Conduct an impact assessment of the regulatory schemes which increase uncertainty at the expense of patient safety, such as PRIME and the medicines approved via conditional marketing authorisation (CMA). Present evidence re: experience with those mechanisms so far.
Ensure early access schemes and conditional MA are not misused as a market access tool where evidence on safety and efficacy is lacking.Ensure CMA is followed by collection of real world evidence and decisions are re-evaluated once sufficient evidence is generated (goal 1.3)

- Regulatory advice and assessments should include the principle of transparency and CoE (all of goal 1)

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**:

In goal 2, ECL appreciates:
- Call for critical assessment of emerging endpoints, particularly increased focus on patient relevant endpoints (quality of life - QoL measures) while ensuring data privacy and security principles are safeguarded
- Collaborative approach toward clinical trials (RCTs) and quality data generation (incl. data standardisation and harmonisation of methods)

ECL calls for:
- Increased transparency of the pharmaceutical system (including scientific advice, RCTs protocols summary and data and anonymised individual patient data (IPD))
Guarantee that RCT data (incl. IPD) are available to the scientific community for re-analysis and use supporting further drug development (goal 2.11)

- Where possible and appropriate, demand superiority trials rather than non-inferiority trials (goal 2.11)

- Where possible and appropriate, demand for comparative RCTs. (goal 2.11)

- Confirmatory studies should elevate patient reported outcomes (PROs/quality measures) and answer clinically relevant questions (e.g., comparative evidence). (goal 2.11)

- EMA should ensure patients, healthcare professionals and payers feel confident new treatments (newly approved substances) work (better) in comparison with existing alternatives (if available). (goal 2.11)

- In case a positive approval is made based on other than significant clinical benefit - OS or QoL improvement, the reasoning for approval shall be clear and publicly available. (2.11)

- EMA should also enforce stricter criteria in post-marketing authorisation trials and surveillance. This includes appropriate study designs and endpoints to close remaining information gaps at the point of marketing authorisation. (2.10)
EMA should be able to withdraw a marketing authorisation in case of worrisome toxicity and safety findings during the post-marketing studies.
Marketing authorisation could be challenged or adapted if post-authorisation data do not confirm assumed benefits on relevant outcomes or in patient groups not covered by the data submitted for marketing authorisation.

- EMA should perform statistical analysis in house on raw data while ensuring the independence and integrity of the process. Such analyses should be available to 3rd parties
Registrational protocols should be made publicly available for comments before the start of the studies (to avoid using suboptimal comparators)
Demand better statistical analysis of observational data (incl. public registration of a detailed study protocol and analysis plan before the start of the study)

- Greater focus on social inequalities, from the perspective of access to treatments for vulnerable populations, not onfly from data but also from access perspective (2.12)

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**:

ECL fully supports the content of the 3rd goal. Particularly:
- Focus on timely access to affordable, high quality medicines
- Ensuring evidence needed by HTA bodies and payers is incorporated in early drug development plans as well as bridging benefit-risk and relative effectiveness assessments
- Collaboration with HTA and payers on horizon scanning for emerging technologies and defining unmet needs
- Enhanced patient involvement and focus on PROs
- Promotion of high quality RWD in decision-making
- Support of greater uptake of biosimilar products

ECL calls for:
- Assessment of best practice and more concrete measures to implement the above points

- Quality measures should serve as primary endpoints in risk-benefit assessment (alongside overall survival - OS). Duration of treatment and necessity for hospitalisation should be also considered in the regulatory assessment. (goal 3.17)

- PRO should be collected via non-bias evaluated questionnaires (3.17)

- Collection of toxicity data as RWD (3.18)

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**:

ECL appreciates focus of current health threats, including (un)availability of approved medicines. The EMA should work together with the European Commission and WHO to investigate the causes of medicines shortages. All challenges causing shortages, including manufacturing issues, market withdrawals, parallel trade etc., should be addressed together with relevant stakeholders. (goal 4.25)

Results of clinical studies should be made available in order to boost repurposing research of marketed products by public research entities. (goal 4.27)

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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**:

ECL finds this goal too general, not bringing new ideas to what was outlined in previous goals. International and cross-sector collaboration should be present throughout the other goals rather than stand on its own. In case it is a stand alone chapter, we recommend to add concrete ideas of collaboration (esp. vs. what is already in place at the moment) and best practices and added value such collaboration brought in different aspects.

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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