Contribution ID: 523cd2f5-5ef8-4355-8beb-f1f23f861562
Date: 28/06/2019 16:58:47

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

* ***Please specify:***

between 1 and 1 choices

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

Name of organisation (if applicable):

Eli Lilly and Company

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.

Eli Lilly & Company (or Lilly) welcomes the opportunity to offer comments on the EMA's Regulatory Science Strategy to 2025 (hereafter referred to as RSS 2025) and applauds this initiative.

Lilly has always pushed the boundaries of science to make conditions that are incurable today, treatable tomorrow. The promise of science to change people's lives has never been greater. Recent progress in understanding biology, including the unlocking of the human genome, has unleashed new insights – allowing scientists at Lilly and our partners more power and precision to treat disease [reference: https://www.lilly.com /]. The EU regulatory system is essential to ensuring that safe, efficacious, and quality new medicines reach patients in a timely manner. As such, the EU regulatory system is viewed as a key enabler for innovation to be incorporated in drug development. All five strategic goals mapped out by the draft RSS 2025 are relevant from our perspective as they identify areas where progress is most needed. At the same time, while agreeing with the objectives' importance, it is essential for the EMA and their stakeholders to focus their expertise and resources in areas that will have the most impact on the effectiveness and efficiency of the EU regulatory system.

Lilly has actively participated in EFPIA's commenting process for the RSS 2025. EFPIA has prioritised the objectives that member companies believe will best enable the delivery of novel medicines to patients – through the most effective, efficient, technologically advanced, informed means possible. As such, Lilly is aligned with the top three priorities outlined by EFPIA as well as with EFPIA's comments in general. Here, Lilly is offering company-specific input and in places where Lilly's comments are directly connected to EFPIA' s feedback, we have added the note of "[reference: EFPIA's comments]".

Lilly appreciates the EMA's active engagement with medicine development collaborators in developing its RSS 2025. Lilly believes that, by continuing its multi-stakeholder engagement, the EMA will be able to implement follow-up actions and achieve its vision: "To underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems".

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.

Clinical trials (CTs) are the basis of drug approvals, confirming the safety and efficacy balance of a medicine. However, both their increasing length and cost are limiting factors to R&D today. At the same time, innovations in recent years are offering opportunities to increase the efficiency and effectiveness of medicine development whilst maintaining high quality data for regulatory decision making. Lilly considers EMA's proposed recommendation with the greatest opportunity for positive impact on the EU regulatory system and in EMA's remit is to "Foster innovation in clinical trials" (Rec 2.2).

CTs should progress on many levels including with their planning, by using complex designs and novel endpoints for instance, and with their operational aspects, once initiated. Further advances in CT design will lead to a transformation of evidence generation in drug development, in which a significant opportunity currently lies in the improvement in digital clinical data generation. This overarching objective encompasses several additional priorities, which relate to new clinical evidence sources (e.g., patient registries, electronic medical/ health records, administrative claims, digital sensors or applications), measures (e.g., endpoints, biomarkers), and methodologies (e.g., Model Informed Drug Discovery and Development – MID3). In particular, the supportive RSS 2025 recommendation "Develop the regulatory framework for emerging digital clinical data generation (Rec 3.3)" is fully supported by Lilly. Progress on this objective cannot be delivered without a multi-stakeholder approach in which patients and sponsors are engaged.

Lilly would propose that the following actions be prioritised for achieving this objective:

- Develop further the CT Information System (CTIS) to best accommodate Complex Clinical Trials. The CTIS should be able to efficiently accommodate managing applications for and the datasets arising from Complex Clinical Trials [reference: EFPIA's comments].
- Advance global coordination on the topic. Important additional Complex Clinical Trials topics should be proposed within ICH for better global alignment on development approaches. For example, ICH has agreed to deliberate soon on the concept of 'Adaptive Designs'; additional elements of Complex Clinical Trials could be opportune for advancement under the ICH infrastructure [reference: EFPIA's comments].
- Consider platform for information sharing. The US FDA MID-3 pilot [Reference: https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program] is viewed positively. Lilly believes that a similar initiative could be initiated in the EU. A pilot may be an effective approach to advance training, broader awareness, and greater consistency across assessors.

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.

Advice from regulators on both scientific and purely regulatory questions is an essential tool for ensuring patients have timely access to innovative, effective and safe medicines. Regulatory input critically informs the process of medicine development, CT design, and resulting data outputs. Timely input into a sponsor's plan maximises the insights gained from CT participants by ensuring optimisation of the development plan. In addition, regulatory advice supports efficient use of the available regulatory pathways, thus reducing the regulatory burden for developers as well as for regulators.

Historically, the development of medicines tended to be relatively linear. However, several recent advances are evolving this linearity, which also requires a rethinking of advice mechanisms within the EU regulatory system. Enhanced regulatory development advice should be timelier and offer tailored engagement of relevant stakeholders based on the questions at stake. As a few examples:

- Use of RWD in the post marketing setting requires consideration and inputs into the plan by regulators and HTA bodies in advance of the medicine's authorisation (e.g. via joint advice)
- Development of medicines with connected devices must be considered concurrently by the developer, which often necessitates coordination of advice from notified bodies, national competent authorities (NCAs) and/or EMA

Lilly favours the EMA proposal of "complementary and flexible advice mechanisms to support innovative product development expanding multi-stakeholder consultation platforms". The flexibility should reside in at least the following three aspects:

o Format: In addition to the existing process, it should be possible to seek timelier advice on more straightforward questions. For instance, a process similar to Japan PMDA's "Pre-meetings" should be considered. This advice mechanism could allow for a swift turnaround with limited administrative onus, and thereby, allow the medicine's development to progress following the deliberation on basic regulatory questions.

o Timeliness: Currently, the time required to gain advice can be quite long in the EU. Therefore, a more iterative, flexible approach could allow the timeline for receiving advice to be significantly reduced in these instances. This option should offer even shorter timelines for follow-up questions (e.g., considering new information or changes to the development programme since the initial advice was given).

o Tailored stakeholder input for medicine-device combinations: It should be possible to seek timely joint advice on medicine-medical device combination products by involving notified bodies, NCAs and/or EMA, depending on the questions. The advice opportunities should also be available for medicine and connected device combinations (although some of these products might not currently require an integrated evaluation pathway, they should be considered holistically whilst designing the development approach). Involving these additional stakeholders would also support the EMA proposal to "Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec. 1.5)". Indeed, it is essential for the developer to gain timely, iterative, integrated input into their medicine-device development plan before implementation.

o Advancing acceptance of digital endpoints: As part of the development of a regulatory framework for emerging clinical data generation, Lilly proposes progressing a platform to gain multi-stakeholder input on digital endpoints. The current processes may be lengthy which is not adapted to the agility sponsors need when determining a CT design. Note: this proposal is also linked to RSS 2025 recommendation to "Develop the regulatory framework for emerging clinical data generation" (Rec 3.3) [reference: EFPIA's comments].

In complement of more flexible advice mechanisms along the development continuum, the EMA should also consider a more iterative guidance approach. The current process to generate scientific and procedural guidelines is extremely valuable as it allows for input from EU-wide expertise through public consultation and /or during workshops. However, due to the often lengthy timelines of the process, finalising guidance may not be timely enough for some rapidly evolving regulatory areas. Therefore, an action for the EMA to consider would be for some guidelines to be supplemented by formal adaptive sections of guidance such as with a Q&A section that could evolve with more frequent updates. If implemented, this adaptable section would more quickly communicate new insights and learnings based upon advancing product experiences, academia/investigators' insights, patients'/clinicians' feedback, other regulators' changes, scientific advice results, product qualifications, stakeholder workshops, etc.

Third choice (h)

18. Promote use of high-quality real world data (RWD) in decision-making

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.

Real-world data (RWD) and real-world evidence (RWE) have the potential to improve patient outcomes and health care delivery by generating new insights, fostering new product development, appraisal and lifecycle management. However, technical guidance, information governance and societal changes are required to utilise the full potential of RWD and RWE in healthcare and in medicines development. Therefore, RSS 2025 recommendation 3.4 should include RWE, for example: “Promote use of high-quality real-world data (RWD) and real-world evidence (RWE) in decision-making”

More specifically, one of the major challenges is how to assess the current sources of RWD as fit for purpose for regulatory purposes. Regulatory agencies should allow existing RWD sources to be used to generate RWE for select regulatory decisions. Any guidance on RWD needs to be integrated with the RWE. Considerations in assessing characteristics of the real-world dataset should support that the data is meaningful, valid, and transparent, and therefore appropriate to answer a specific regulatory question in a particular clinical context (i.e., fit-for-purpose).

Building on this premise, any future guidance intended to describe the role of RWE, specifically observational studies, in informing regulatory decisions should leverage the experience that already exists in the field. Guidance should reference and endorse existing guidelines for the conduct and reporting of observational research studies. Guidance should outline expectations for study protocol and statistical analysis plan, the reporting of technical study details, and required procedural practices. It should also acknowledge that suitability of data source, study design, and analytic choices are highly dependent upon clinical or regulatory context and that it may therefore require expert assessment on a case-by-case basis. Finally, guidance should outline the standards/criteria for the relevance and reliability of secondary, retrospectively analysed data sources.

Therefore, Lilly supports the actions outlined by EFPIA, namely:

- Launch a strategic initiative to integrate RWE in drug development, including the use of demonstrator projects to engender familiarity [reference: EFPIA’s comments].
- Building on ongoing efforts (in EU and internationally), to provide clarity on scope and quality of sources of RWE, recognising governance and resources required for these sources and identifying where gaps exist [reference: EFPIA’s comments].
- Seek to align and contribute to extend the standards and methodologies for collecting, analysing and validating RWE use internationally [reference: EFPIA’s comments].
- Coordinate workshops to progress dialogue and publish workshop conclusions [reference: EFPIA’s comments].

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

In Lilly's view, one element missing from RSS 2025 is the mechanism to evolve cGMP (continuous Good Manufacturing Practices). Today, there are pathways to introduce new manufacturing technology as part of a specific dossier or based on a molecule change. However, there are no clear mechanisms to evolve the GMPs for technology that are not product specific. The industry is on the cusp of many new technologies, some of which will not be dossier specific (e.g. new ways to monitor sterile areas, use of robots) and will need modification of the associated cGMP. Currently, sharing information about these topics is limited to presenting at conferences. As such, the regulatory acceptability may be subject to the decision of an individual inspector rather than via collective regulatory views. The official GMP updates lag the scientific capability, which may result in manufacturers not investing in new manufacturing technology due to uncertainty regarding GMP acceptability (unclear at time of investment decision). It would be beneficial to have a clear regulatory pathway for technology changes affecting a platform of products or sites, instead of a single dossier. Another option could be a mechanism to raise proposals to change the GMPs with a formal response mechanism.

In addition, an objective should be added around regulatory optimisation of existing IT tools and associated technologies. There is opportunity to improve the existing systems and databases, so both regulators and industry can optimise their value and reduce the collective administrative burden. For instance, if feasible under the current legislation, some purely administrative changes could be submitted using the Article 57 database (also known as the "eXtended EudraVigilance Medicinal Product Dictionary" (XEVMPD). If practical, this objective could advance under collaboration with other groups e.g. the HMA Regulatory Optimisation Group.

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 addition to the above-mentioned second ranked top priority “Diversify and integrate the provision of regulatory advice along the development continuum” (Rec. 1.7), Lilly considers that “Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products” (Rec. 1.5) is another area that would have significant impact on the EU regulatory system. As such, Lilly is fully supportive of the development of such a pathway. The details of the pathway should be drafted in collaboration with relevant stakeholders (e.g. through a multi-stakeholder workshop) and tested via a voluntary pilot process. Most importantly, it should be initiated relatively soon to allow a timely and smooth implementation of the Regulation (EU) 2017/745 on medical devices.

Regarding the recommendation “Promote and invest in the Priority Medicines scheme (PRIME)” (Rec. 1.3):
- Lilly proposes to add the action to allow the PRIME scheme for products already licensed in the EEA (i.e., new indications) that could address unmet medical need. Indeed, it is essential to focus on lifecycle activities that are also providing new therapeutic options for unmet medical needs.
- Lilly suggests broadening the PRIME action “Shorten the time between scientific advice, clinical trials and MAA submission” to submission or line extension/new indication, based on the same principle as above.

Regarding the recommendation “Facilitate the implementation of novel manufacturing technologies (Rec. 1.4)”, Lilly considers that these initiatives should also be available post-approval.

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**:

Please refer to Question 5 since Lilly's top priority is the RSS 2025 recommendation "Foster innovation in clinical trials" (Rec. 2.2) which, in Lilly's view, encompasses the recommendation to "Develop the regulatory framework for emerging digital clinical data generation" (Rec. 2.3).

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**:

Lilly supports initiatives that aim at resolving how to best incorporate patient insights into regulatory decisions. Please refer to Question 5 on the third top priority regarding the recommendation “Promote use of high-quality real-world data (RWD) in decision- making” (Rec. 3.4).

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**:

Lilly is overall supportive of the recommendations outlined in Strategic Goal 4. The ability to introduce manufacturing changes globally increases efficiency and modernises process, which can help assure medicine supply. Therefore, global alignment is essential to the efficiency of these measures. Regarding the recommendation “Promote global cooperation to anticipate and address supply challenges” (Rec. 4.3), Lilly considers that the action to “Improve post-approval change mechanisms” should be added.

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