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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

* ***Please specify:***

between 1 and 1 choices

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

Name of organisation (if applicable):

MSD

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.

MSD welcomes the draft RSS 2025 shared by EMA for consultation and we are grateful for the chance to respond. MSD has actively contributed to responses by our industry trade associations, for both our human and animal health. We focus our company comments on the elements of the human health strategy which have a distinct bearing for our science and our business. MSD offers a unique perspective in terms of scope, with activities in human health, animal health, preventative (vaccines) and therapeutic treatments, including antimicrobial treatments.

This consultation is very timely. The EMA, the EU Regulatory Network and biopharmaceutical innovators, like MSD, are facing a challenging future where some of the most demanding science will need to be achieved in increasingly cost-constrained circumstances for the public sector and for industry. At the same time, this substantial investment in science will deliver novel technological solutions to address some of humanity's most threatening disease burdens by using novel clinical and evidentiary methods. These trends establish the importance of the Regulatory Science Strategy to 2025 (hereafter RSS 2025) for Europe to prepare for these challenges in the context of a competitive global environment.

We can see how the RSS 2025 can marshal efforts to address the most important regulatory science opportunities for the next 5 – 10 years. However, as with any strategic programme, there is a tension between delivering on performance today and changing the performance potential over time. We have considered this tension carefully, as an active user of EMA's services (in 2018, MSD's regulatory submissions accounted for 6% of positive Opinions and 12% of New Active Substances approved) (1). With EMA's budget at roughly one-quarter that of the FDA's and staffing one-eighth (2), despite the extended working teams in the National Competent Authorities, it is unclear how the RSS 2025 plans could be implemented with impact without consideration of additional resources required. We encourage EMA to discuss these practical but essential aspects with the European Commission and the Member States as part of the commissioning of the strategy.

We also encourage EMA to consider this tension more explicitly in its final prioritization and planning for the delivery of the RSS 2025. As directed in the consultation (3), we present here the top 3 priorities outlined in the strategy which we believe will have the greatest potential impact for our science and our business. They are:

- Foster innovation in clinical trials (Rec 2.2).
- Support developments in precision medicine, biomarkers and 'omics (Rec 1.1)
- Diversify and integrate the provision of regulatory advice along the development continuum (Rec. 1.7)

MSD supports EFPIA's Proposals to Action and Deliver RSS 2025:
To foster innovation in clinical trials (Rec. 2.2):
- Develop a new strategic initiative to broaden the use and acceptability of complex innovative CTs
- Deliver engagement opportunities and pilot schemes to learn from case studies, reflecting range of complex study designs;
- Develop further the CT Information System to best accommodate complex CTs;
- Facilitate better alignment between EU regulators in the clinical trial pathway; and
- Advance global coordination on the topic.

To diversify and integrate the provision of regulatory advice along the development continuum (Rec. 1.7):
- Lead the redesign of a more flexible and integrated R&D product support mechanism;
- Enhance coordination of advice across Committees, National Competent Authorities, pertinent stakeholders;
- Provide preliminary feedback to the sponsor ahead of discussion meetings;
- Ensure wider stakeholder involvement;
- Consider special perspectives within the advice continuum;
- Optimise usage of CT Information System (CTIS); and
- Advance acceptance of digital endpoints.

To promote the use of high-quality RWD in decision making (Rec. 3.4):
- Launch a strategic initiative to integrate RWE in drug development, (ie demonstrator projects);
- Build on EU, international ongoing efforts on scope and quality of sources of RWE;
- Align and contribute to extend the standards and methodologies for collecting, analysing and validating RWE use internationally; and
- Drive RWD/E dialogue and publish workshop conclusions.

Moreover MSD adds to this list in order to support developments in precision medicine, biomarkers and 'omics (Rec 1.1) actions for EMA such as:
- Bilateral/multilateral statistical workshops for biomarker qualifications and subgroup analyses
- Early scientific advice procedures for biomarker qualification

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(1) EMA Annual Report 2018; company figures.
(2) Ibid; for EMA 2018 figures. € 317 billion and 836 staff. FDA Budget Summary (2018); figures drawn from 2016 final reporting and refer only to human drugs and biologics. 2016 budget was $1.43 billion or € 1.34 billion and 7,022 staff.
(3) EMA Regulatory Science to 2025

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.

MSD has pioneered novel approaches in clinical study design and methods that more accurately address the core research questions that establish the value of a new medicine and/or indication of use. We are often challenged by the underlying disease and human biology to consider more sophisticated ways of ascertaining the scope of the value to be achieved in terms of patient and healthcare benefit. For example, MSD was the first company to be awarded tissue-agnostic/site-agnostic approval (1), an indication which has since been approved in most of the world (not Europe) and followed by other manufacturers. This process innovation requires a concomitant process innovation in regulatory science.

Likewise, the range of sources of data to include in clinical trials continues to advance with opportunity (e.g. new digital technologies) and with need (e.g. the need for more patient-relevant outcomes). Practical challenges in assessing benefit over time and study populations will require greater blending of approaches (e.g. combining RCT and RWE, pragmatic trials) as well as methods (e.g. novel imaging techniques, passive data collection using monitoring technologies). What will not change is the quality standards of evidence required to establish benefit: risk, and for this, it will be imperative for EMA to engage not only sponsors by all stakeholders within Europe and internationally.

By prioritizing this recommendation, EMA will be able to advance innovative clinical trial concepts (e.g., umbrella, basket, adaptive seamless design, master protocol or pragmatic trials, trials in small populations) which are instrumental to bring novel medicines to patients efficiently and effectively. This would also afford

an opportunity to address some of the current inflexibilities in the provision of scientific advice and regulatory approval system for CT applications. Importantly, this recommendation encompasses some of the other priorities, which relate to new clinical evidence sources (e.g., registries, RWD, Big Data), outcome measures (e.g., endpoint, biomarkers), and methodologies). We identify here the recommendations we see as interdependent and reinforcing to innovation in clinical trials.

Supporting Recommendations:

- Develop the regulatory framework for emerging clinical data generation (Rec 3.3)
- Support developments in precision medicine, biomarkers and 'omics (Rec 1.1)
- Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec 1.5)
- Reinforce patient relevance in evidence generation (Rec 3.3)

MSD supports the actions proposed by EFPIA:

- Implement a new CCTs strategic initiative. Westrongly encourage the Agency to develop a new strategic initiative to broaden the use and acceptability of complex innovative clinical trials based on global experiences so far and with the support of all relevant stakeholders and experts (
- Organisation of dedicated multi-stakeholder collaborations (e.g., workshops, demonstration projects and pilot schemes) to raise awareness, share case studies and learnings, and identify best practices. The Agency has previously hosted a number of successful workshops with industry to progress important topics such as modelling & simulation, dose-finding studies, and paediatric extrapolation. CCTs workshops would facilitate the use and acceptability of innovative tools and methods to be used in drug development. Workshops would also ensure that emerging challenges in conducting CCTs can be addressed in a timely way (e.g., concurrent multiple substantial modifications to CTs) and in using the resulting evidence in filing (e. g. tumour-agnostic indications). RThese workshops could also include global regulators (e.g., FDA, PMDA, Health Canada).
- Facilitate better alignment between EU regulators and stakeholders in the clinical trial pathway. These types of fora should help resolve alignment issues across National Competent Authorities, ethics committees, HTA bodies and patients' organisations when considering acceptance of CCTs. Experience should also be gained through multi-stakeholder collaborations such as demonstration projects (e.g. through public-private partnership platforms).
- Develop further the CT Information System (CTIS) to best accommodate CCTs. The CTIS needs to be able to efficiently accommodate managing applications for and the datasets arising from CCTs.
- Advance global coordination on the topic. Important additional CCTs topics should be proposed to ICH for better global alignment on development approaches. For example, ICH has agreed to deliberate soon on the CCT concept of 'Adaptive Designs' and additional elements of CCTs could be opportune for advancement under ICH.

(1) https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature

Second choice (h)

1. Support developments in precision medicine, biomarkers and 'omics'

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.

Our collective goal is to continue to better precise treatments and interventions for the needs of a given patient, so that we maximize the potential benefit and minimize any risks of adverse events. How we do this needs to be established through scientific process, clinical validation and stakeholder acceptance. EMA

anticipates this process in its proposed actions in the RSS 2025, in terms of biomarker qualification, 'omics' methods across the development lifecycle and engagement with 'downstream' decision makers and patients.

There is an opportunity to substantially evolve the EMA's biomarker validation process in order to encourage greater uptake and use. This is important also across regions, as our evidence development plans are global. Beyond the use of these biomarkers in regulatory decision making, there also needs to be greater alignment with HTA bodies, which often challenge biomarkers in use and can delay patient access to innovative personalised medicines. Dedicated expert group discussions, routed in the reality of clinical practice, would help EMA and downstream regulators to align their views.

We also note the work to date by EMA with regard to analytics, including post-hoc subset analyses guidance published in 2019 (1). This area for regulatory science is a priority and we welcome the attention; however, these methods can inadvertently lead to a loss of validity of randomization, an introduction of bias and potentially difficulties in replicability. There is need for greater scientific exchange over the statistical science that underpins regulatory decision making, and MSD would welcome further discussions on these topics in bilateral meetings or broader workshops.

Supporting Recommendations:

- Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec 1.5)
- Diversify and integrate the provision of regulatory advice along the development continuum (Rec 1.7)
- Foster innovation in clinical trials (Rec 2.2)
- Develop the regulatory framework for emerging clinical data generation (Rec 2.3)
- Optimise capabilities in modelling, simulation and extrapolation (Rec 3.6)

MSD proposes the following actions for consideration:
- Bilateral and multilateral statistical workshops to better establish the basis for these biomarker qualifications and subgroup analyses.
- Qualification pathways for biomarkers should begin with early scientific advice procedures, including via broad scientific advice.

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(1) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf

Third choice (h)

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

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.

Just as EMA seeks to better connect the different decision-making steps across the life cycle of a medicine, so we need to link up advice across the EU regulatory ecosystem. Providing enhanced advice options with greater flexibility in the delivery of this advice is needed to reflect the changing pace and process of innovation along the development continuum. This enhancement of advice needs to integrate paediatrics in the development support provided by EMA, including clinical trials and scientific advice supporting licensing applications. Integrated advice also must include manufacturing as well. Innovation in manufacturing continues, with new manufacturing and control methods under development; applicants require greater access to advice on manufacturing control aspects to ensure timely alignment and understanding, and this

could be achieved through enhanced dialogue with the EU PAT team.

Moreover, this broadening and integration of regulatory advice needs to go beyond the EMA programmes (eg PRIME) to bridge the advice and decision-making gap across the EU regulatory system (i.e., EMA, EMA' s Committees, National Competent Authorities) and beyond (e.g., US FDA). Instead of companies trying to piece together advices given at multiple points in the drug development and manage conflicting views, the process needs to bring these advisors and decision-makers together in a more holistic offering. The overall value of pan-EU scientific advice is undermined when contradictory opinions emerge during the development of a product. This national approach to clinical trials and the EU centralised approach to the provision of scientific advice also mean that there is no unified "line of sight" on the progress of a product during its development from early clinical trials through to approval. This contrasts unfavourably with the U.S. IND system where the FDA provides comprehensive guidance to companies. Early appointment of a Rapporteur, as in PRIME, may be an ideal method to help facilitate flexible, iterative, but integrated regulatory advice, as can engagement with other decision makers (HTA and Notified Bodies).

Supporting Recommendations:

- Reinforce patient relevance in evidence generation (Rec. 3.3)
- Contribute to HTA's preparedness and downstream decision making for innovative medicines (Rec 3.1)
- Promote and invest in the PRIME scheme (Rec 1.3)
- Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec 1.5)

MSD supports the actions proposed by EFPIA:

- Redesign of a more flexible and integrated R&D product support mechanism, providing agile dynamic advice across the lifecycle of the medicine. Research and development timelines are becoming increasingly efficient and should be matched by the timelier provision of advice. The developer should have the ability to select from multiple levels of advice engagement based on the attributes of a particular product.
- Integrate the opportunity for iterative CMC data submission during review. This proposal can be achieved by delegation of advice and review of dossiers by relevant Working Parties (e.g. BWP for biologics, MSWP for M&S, Biostats WG).
- Enhance the coordination of advice across EMA Committees, National Competent Authorities and other pertinent stakeholders. Ensure closer alignment of understanding between EMA and national regulators to minimise any conflict in views between centralised scientific advice and CTA assessment.
- Provide preliminary feedback ahead of discussion meeting so that the sponsor can also suggest additional topics for discussion based on this feedback. In this way, the developer's discussion topics can be added to those determined by the SAWP/HTA bodies (i.e., a more interactive engagement process between the sponsor and the SAWP).
- Ensure wider stakeholder involvement in specific aspects of advice (e.g., CTFG for clinical trials, Notified Bodies for device/drug products)
- Within advice continuum, consider special perspectives for different types of products (e.g., paediatrics, drug-device combination products)
- Optimise usage of CT information System. Consider how the data to be included in the CT Information System – currently being developed as part of the CT Regulation - implementation can be better used across the EU Medicines Regulator Network so that national regulators have that full harmonised insight into the clinical data generated on a product during its development even when the clinical studies on the product are not being performed in that Member State.
- Advance acceptance of digital endpoints. A platform to achieve multi-stakeholder input on proposed digital endpoints should be developed. One current option is the qualification opinion/advice, however this is a lengthy process that is not adapted to the agility sponsors need when deciding on a CT design.

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

Although the relevance to post-authorisation regulatory and safety science is implicit in many of the recommendations, it would be valuable to make these links more explicit in the texts as well as the underlying planned actions. To do so will underscore the lifecycle approach to innovation that the Agency is taking for regulatory science.

For example, the recommendation Expand benefit-risk assessment and communication (Rec. 2.4) identifies the need for systematic application of structured benefit-risk methodology and quality assurance systems across the network, including improved communication with HTA bodies. However, this could be elaborated also to consider post-authorisation assessment, considering new evidentiary sources and the need to improve the analytics and evaluation of these data to better identify and isolate meaningful safety signals for action.

Finally, greater focus on EMA's support for health literacy would also be valuable to introduce. The RSS 2025 puts patients at the centre for the agenda, and we support this approach. However, for patients to be able to fully play a part and benefit from these initiatives, health literacy needs support. According to the European Health Literacy Survey, Nearly half of all Europeans have inadequate and problematic health literacy skills (1). Special attention could be given to developing local networks and communication tools which can deployed across a range of channels with special consideration given to digital literacy and the ability of populations to reach the content.

(1) Roediger, A et al (2019) "Nothing about me without me: why an EU health literacy strategy embracing the role of citizens and patients is needed" Archives of Public Health, https://doi.org/10.1186/s13690-019-0342-4

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:

This Strategic Goal includes several recommendations and actions that MSD at would rank highly important and important, which reflects the centrality of this goal to the regulatory process of translating valuable science into valued medicines and treatments.

Our rankings are as follows:

Very Important:

- Support developments in precision medicine, biomarkers and 'omics (Rec. 1.1); as previously discussed.
- Facilitate the implementation of novel manufacturing technologies (Rec 1.4).

Without the development and implementation of novel manufacturing technologies, innovative potential for new and better treatments will be limited. This is not only the case for technologies like cell and gene therapies, where manufacturing is core to the novel treatment; but even for established products, novel manufacturing technologies (like continuous manufacturing) may be able to offer advantages in flexibility, quality and reliability that could yield great benefits for healthcare systems and patients. MSD would likewise

welcome a focus on the use of more advanced analytics and modelling, as well as early, flexible scientific advice (e.g. EU PAT Team), to support these innovations in manufacturing technologies.
Dialogue between Industry and regulators on technical adaptation of the current regulatory framework is ongoing at the EMA and ICH level. A more flexible and continuous mechanism of advice is desired which will allow specialised experts in the EU Network to understand more deeply the end-to-end process and innovative multivariate analysis that guarantee the product quality. Further, it would be beneficial to have a clear regulatory pathway for technology changes affecting a platform of products or sites, rather than just one dossier.

- Diversify and integrate the provision of regulatory advice along the development continuum (Rec. 1.7); as previously discussed.

Important:

- Support translation of Advanced Therapy Medicinal Products cell, genes and tissue-based products into patient treatments (Rec 1.2) Although the first advanced therapy medicinal products have been approved, fewer have approved by HTA bodies / reimbursement bodies and are actively in use for the treatment of patients in Europe. We support the actions proposed under this Recommendation and would add to this the importance of engagement with the general public, to improve the public understanding of science of ATMPs.
- Promote and invest in the PRIME scheme (Rec. 1.3); The PRIME scheme needs to allow for participation of all applicants from an early stage of development (i.e., at proof of principle stage) and should be applicable for the extension of indication, based on the same criteria as for an initial first indication and with aligned opportunity for accelerated assessment A “fast lane” approach could be designed for PRIME products which would include: shorter timeline for eligibility and kick-off meeting, continuous access to EMA contact person, dynamic opportunities to receive advice on product development, including rolling submissions of data. Input for regulatory process innovation can be drawn from the 2018 EMA/FDA PRIME workshop in London.

Recent trend data demonstrate that EMA’s product review timelines are getting longer, and indeed, are notably longer compared with US (1). The first marketing authorizations for products designated as eligible to PRIME were granted only in June 2018; hence it is essential to review the performance of the scheme after 3 and 5 years, to ensure that it delivers the expected impact on public health (i.e. faster priority medicines to market).

- Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec. 1.5); Together with EFPIA, MSD strongly supports the proposal to create an integrated evaluation pathway for medicine-medical device combination products and for medicines that are developed and used in combination with companion diagnostics. Indeed, expertise needs to be enriched to enable adequate risk/benefit assessment of such products. In parallel of developing this evaluation pathway, it is essential for the developer to have the possibility to gain acceptance of their development plan before it is implemented. It should therefore be possible to ask for development advice from the stakeholders involved in the assessment of these products. By design, this platform should allow for timely joint advice, involving notified bodies, NCAs and/or EMA, depending on the type of questions.

Moderately Important:

Relatively lower priority is given to the recommendation on nanotechnology and new materials in pharmaceuticals primarily because these areas are already reflected in ongoing initiatives by EU regulators.

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(1) Centre for Innovation in Regulatory Science; R&D Briefing 70; New drug approvals in six major authorities 2009-2018: published 29 May 2019

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**:

"Collaborative evidence generation" as a theme for this Strategic Goal demonstrates both the opportunities and the challenges for establishing the value of a medicine or treatment over time. It highlights that data - and the evidence these data support – are distributed. No one source of relevant data exists, and these data sources are gathered, created and decommissioned over time and globally. The assessment of these evidentiary sources is also distributed, and assessment is undertaken in accordance with the preferences and frameworks of the decision-maker. The scientific quality of evaluations is in the eye and mind of the beholder. EMA has a critical role to play in creating some order and process in the methodologies and practices of evidence generation, within Europe and globally.

Our rankings are as follows:

Very Important:

- Foster innovation in clinical trials (Rec 2.2); as previously discussed.

Important:

- Develop the regulatory framework for emerging digital clinical data generation (Rec 2.3); Digital tools are only as useful as the data they provide can be harnessed for better understanding and decision-making. Investments are needed to work on the technical and social infrastructure needed. Moreover, these investments will need coordination, so there is an imperative to have key partners, including industry, around

the table. Patients also must be considered in this regard, and with this the digital aspects of health literacy that will have a bearing on their ability to participate and engage.

- Expand benefit- risk assessment and communication (Rec 2.4) Health literacy remains a key policy priority for MSD, as we believe that patient centricity works best if patients are empowered to engage in the decisions about their health. Although 'health literacy' is not explicity addressed here, we believe it underpins the actions to incorporate patient preferences and individual data in the benefit-risk assessment as well as the communication efforts of these assessments to patients, HTA bodies, payers and the general public. Digital literacy disparity may become an obstacle in selecting the right channels and ensuring proper reach.
- Optimise capabilities in modelling and simulation and extrapolation (Rec 2.6); Amassing data is of no value unless it can be interrogated by methods that generate evidence that can better support decision-making. MSD is investing substantially in advanced computational methods and modelling to deliver greater insights from our data and to better direct our efforts on where to build data in future. EMA must do the same; however, EMA also has a further requirement to align these approaches with regulators globally. Together, we need to establish standards with all stakeholders to create a framework that minimizes duplication and yet also allows sufficient flexibility for innovation, given the emergent state of this science and technology.
- Exploit digital technology and artificial intelligence in decision- making (Rec 2.7); Although it is too soon to see examples of "strong" AI in evidence in drug development or regulation, early efforts to introduce machine learning are finding purchase in regulatory activities in companies. These solutions could provide key opportunities for EMA to optimize resources to focus on the highest value-added activities. This will require new skills and resources for us all.

Moderately Important:

- Leverage novel non- clinical models and 3Rs (Rec 2.1); there is work ongoing to identify better approaches in the EU and internationally. Nevertheless, EMA is encouraged to continue collaborating, and MSD, together with EFPIA, is pleased to offer support as appropriate
- Invest in special populations initiatives (Rec 2.5); EMA is encouraged to continue its current efforts to support drug development for special populations and improve patients' early access through appropriate research. For these patients with often a high unmet medical need, whether children or the elderly, it is crucial to optimise drug development knowing that new tools and methods (e.g., M&S, RWD, use of wearables, registries) could help generate data from these patients where feasibility of standard randomised CTs is known to be challenging.

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**:

We recognize the need to improve timely access to valued and needed treatments for patients, and regulatory review is a foundational step in that process. Although access is often frustrated at later decision stages in pricing and reimbursement, EMA must advance regulatory procedures with greater patient-centricity.

Our rankings are as follows:

Very Important:

- Promote use of high-quality real-world data (RWD) in decision making (Rec. 3.4); In RSS 2025, the EMA anticipates the use of high quality RWD as complementary evidence which may be used in decision making. To be able to build a consensus for this with all stakeholders, we need to address RWD in the context of the novel sources (including digital) that may be used as a source, the global standards and methodologies necessary to ensure quality and fidelity of data, and the novel analytical techniques (e.g. AI, modelling) which ultimately is needed to generate the explanatory value of the RWD. Acceptability builds from familiarity, and this suggests a key role for experimentation in EU. Simply put, we need more pilots and less paper. T Our collective goal must be to deliver fit for purpose RWD/RWE that can deliver greater value for regulatory decision making.
- Deliver improved product information in electronic format (ePI) (Rec. 3.6); ePI will benefit not only patients, their carers and healthcare professionals through better tailored communication; it will also benefit the healthcare system with the flexibility ePI can provide supply chains to support availability. Health literacy

aspects should be recognized, as ePI can facilitate formatting that is more patient-centric and additional languages. MSD believes that Europe is at a tipping point to take this recommendation from theory to practice, and we urge EMA and HMA to work with stakeholders, like the Inter-Association Task Force (IATF) which MSD has the honour to chair, to develop practical pilots. These pilots can deliver clarity on procedural requirements, practical logistics and societal engagement and preparation.

Important:

- Develop network competence and specialist collaborations to engage with big data (Rec. 3.5); Closely linked with Recommendation 3.4 on RWD, MSD, together with EFPIA, recognizes the need for concomitant investment in the skills and networks to undertake analytical work with Big Data to support regulatory decision-making. This priority has also been identified in the HMA-EMA Big Data Taskforce Summary Report.
- Contribute to HTA's preparedness and downstream decision making for innovative medicines (Rec. 3.1); EMA's years of engagement with HTA bodies have delivered progress and fostered a better mutual understanding of evidentiary standards, methods and assessment, whilst "respecting the remit and perspectives of all sides." (p. 22, RSS 2025). There is still much to be done, particularly in balancing the challenges of matching a global development programme with a variety of local healthcare system needs.
- Reinforce patient relevance in evidence generation (Rec. 3.3);. Following on the substantial progress to date, the big step to take now is on how to include patients more directly in the definition and collection of the evidence itself, which also links to the recommendation 3.4 on RWD. Again, health literacy underpins this agenda.

Moderately Important:

- Further develop external engagement and communications to promote trust and confidence in the EU regulatory system (Rec. 3.8); Without question, trust and confidence in the EU regulatory system is a sine qua non for the delivery of the RSS 2025, but also the effective performance of the EMA and EU regulatory network as it is today. The key message is that this action is essential; but it stands outside of the RSS 2025 per se.

Less Important:

MSD has given less priority to initiatives which are better addressed to procurement decision-making, which should be undertaken by other agencies at the EC and national level:

- Bridge from evaluation to access through collaboration with payers (Rec. 3.2). Regulatory processes and assessments should maintain their distinctiveness from decision making for different purposes (pricing, terms of access). The opportunity for determining the value of a medicine in healthcare is also important but it follows that important regulatory decision; and the payer's assessment is appropriately based in the specific context in which healthcare is delivered. Greater explanation of the benefit:risk assessment and its bearing on clinical effectiveness would be helpful for all decision-makers, including payers.
- Promote the availability and support uptake of biosimilars in healthcare systems (Rec. 3.7); EU regulators have pioneered the biosimilar regulatory pathway, the principles of which have been replicated and adopted around the world. However, the promotion of the availability and uptake of biosimilars in healthcare systems is not a regulatory science topic.

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**:

This Goal aligns very closely with MSD's own objectives to deliver new and much needed vaccines and antimicrobial treatments in readiness to address emerging health threats globally. We are relatively unique amongst the biopharma companies in addressing the full complexity of these issues in our business, whether we consider vaccines, antibiotics and supportive treatments for both human and animal health. We also recognize the needs to better support the supply chain in these different settings to allow fast and flexible response to health needs, emergency or chronic
Most of the core recommendations with this Goal are "must do" activities for EMA, as a globally leading regulatory agency, and the EU regulatory network with responsibility for over 500 million people across 31 countries (EU and EEA). This suggests the need to clarify what initiatives are undertaken as part of RSS 2025 and what comprises the EMA's standing operational plan, and what implications this has for resources and timing.

Very important
• Support innovative approaches to the development, approval and post-authorisation of vaccines (Rec. 4.4); EMA has a critical role to play in enabling new vaccines to become developed and accessible to the populations in need. We believe that the advancement of methods/tools (e.g. biomarkers) to characterise immune response should facilitate the identification of correlates of protection and surrogate markets and support the development of new approaches (e.g. in vitro methods to identify measurable characteristics of safety, quality and potency). The potential to promote innovative clinical trial design will allow manufacturers to demonstrate positive benefit:risk with a reduced number of subjects recruited for Phase III trials. Both of these actions will expedite innovative development.

MSD piloted the first parallel scientific advice between EMA, HTA bodies and NITAGs because we strongly support the need for better understanding and engagement of assessment and decision-making

requirements that each body requires. Collectively, this will streamline the evidence generation process, which then also needs to be considered for the post-marketing setting. We support the establishment of a post-approval EU benefit:risk monitoring, providing cooperation between regional and national surveillance networks to generate meaningful data efficiently. Finally, as the WHO has noted, vaccine hesitancy is significant health risk for EU citizens, it has been driven by insufficient health literacy levels combined with susceptibility to misleading information. Special attention should be given to developing local networks and communication tools which can be deployed across a range of channels to rebuild trust in vaccines.

Important:

- Continue to support development of new antibacterial agents and their alternatives (Rec. 4.2); MSD welcomes proposals to support the development of new medicines to combat AMR, and we note with great interest the new opportunity offered by EMA to target Innovation Task Force meetings for antibacterial candidate treatments. However, further regulatory support for antibiotic development, which offers the support and potential to expedite assessment along the lines of PRIME, is still needed to bring these needed treatments more quickly online.

The key challenges for antibacterial agents are also in the “demand side” of the equation, both with regard to effective stewardship and critically sustainable markets for these much-needed treatments. The proposal for EMA to work with HTA bodies to define and explain the relevance of evidence requirements for new antibacterial medicines is much needed. We must also recall the importance for development of better diagnostics to improve stewardship and limit diseases.

- Promote global cooperation to anticipate and address supply problems (Rec. 4.3); We agree strongly with the explanation in the RSS 2025 that the reasons for unavailability are complex and based within a global supply chain framework. The complexity reflects the fact that only some reasons have a regulatory dimension, and so it is not entirely within the remit of EMA to address these. However, there are opportunities to act. We welcome the setting up of a pilot phase when HMA/EMA guidance on shortage notification will become effective. Having a pilot phase is essential to work through these processes and ensure supply chain management adjusts smoothly.

Where reasons are more related to procurement terms, it is therefore important to continue to engage with health authorities on the causes of supply shortages, as indicated in this recommendation. We would also link this recommendation to two others: Recommendation 1.4 (novel manufacturing technologies) and (Recommendation 3.6 (electronic product information ePI), both of which could offer flexibilities in the supply chain to better address the causes for unavailability of medicines.

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**:

Without question, RSS 2025 Strategic Goal 5 as an essential enabler for numerous recommendations under the previous goals. It also is the feature of the RSS 2025 which will distinguish it from previous 5-year plans: it recognizes the important role that academia needs to play in refreshing and strengthening regulatory science in Europe. Academia can do this through its research activities, but it will also do this through its teaching. The pipeline of qualified graduates who will take their place in the regulatory bodies and roles within companies like MSD, will greatly benefit from the close proximity of research, “triple helix” (7) engagement and teaching.

Consequently, although the goal and the recommendations as described in the consultation document seem to focus narrowly on the engagement between regulatory authorities and academics, industry also recognise the value of this goal. Moreover, MSD, together with other industry colleagues, would recommend that to truly achieve the goal of enabling and leveraging research and innovation in regulatory science, both academic and industry-based researchers should be acknowledged in this strategy. To include industry as a partner in these efforts will ensure a richer elaboration to outline and collaboration to advance the research horizon.

Important:

• Develop network-led partnerships with academia (Rec. 5.1) – The development of network-led partnerships between academia and regulators – to which we would add pharmaceutical industry researchers – would create the platform to undertake fundamental research in strategic areas of regulatory science. This measure can support platforms for scientific discourse and engagement including through IMI and beyond. This proposal could also be extended to include collaboration with students, as it is critical for Europe to have a pipeline of talent to support the long-term future of regulatory science.

• Disseminate and share knowledge, expertise and innovation across the regulatory network and its stakeholders (Rec. 5.4): As a key contributor to scientific advances, industry would appreciate involvement in opportunities the exchanging of knowledge and sharing of expertise.

Moderately Important:

• The other two recommendations are important, but the priority is given to 5.1 and 5.4 because they are necessary to establish for the other two recommendations to come to fruition. Leverage collaborations between academia and network scientists (Rec 5.2) also includes some welcome focus on ring-fencing investment for emergent scientific challenges; however, focusing on the link only between network scientists and academia to provide translation from applied research into new drug products and regulatory tools seems too narrow a focus. Industrial researchers could play a material role in supporting EMA and academia to stay at the cutting edge of these emerging innovations.

• Identify and enable access to the best expertise across Europe and internationally (Rec. 5.3): This recommendation is key to review complex and innovative dossiers.

Anything missing

The role of industry (e.g., pharmaceutical and information technology companies) in this community of research and practice should be noted, to ensure that "regulatory science remains at the cutting edge so that EMA can deliver its fundamental mission of protecting human and animal health and facilitating the availability of medicines to patients" (p. 32, RSS 2025). Any strategy to advance regulatory science related to medicines should include the principal contributors, including medicine developers.

Proposed specific actions

• Include pharmaceutical industry researchers in the network-led partnerships that direct priority areas for fundamental research based on the regulatory science strategy (e.g., PROs, 'omics, AI, drug-device combinations, M&S).

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(2) Henry Etzkowitz, Loet Leydesdorff, (2000) "The dynamics of innovation: from National Systems and "Mode 2" to a Triple Helix of university–industry–government relations", Research Policy,Volume 29, Issue 2, Pages 109-123.

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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