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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):

H. Lundbeck A/S

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.

"Mental and neurological disorders, or "disorders of the brain" are becoming more prevalent over time and are threatening not only the quality of life of millions of European citizens but are also creating major challenges for the EU's capacity to achieve the goals of its Europe 2020 strategy on economic growth and job recovery.
Brain disorders are complex and interlinked with hundreds of specific diagnoses, codified in diagnostic classifications systems (currently under revision WHO International Classification of Diseases, ICD-11 and American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-V). Until recently, brain disorders were associated with disciplinary fragmentation in research and practice, using different concepts and approaches. There is today greater awareness on their common denominators, burden and challenges to manage them in a more integrated approach, and even to prevent some of them." (1)

H. Lundbeck A/S ("Lundbeck") appreciates the opportunity to comment on the EMA Regulatory Science Strategy. Our response is in line with the joint response of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and therefore will not repeat points made by EFPIA but rather aims to complement the joint industry response with aspects specifically related to CNS (central nervous system), which is our area of expertise.

About Lundbeck
Lundbeck is a global pharmaceutical company highly committed to improving the quality of life of people living with brain disorders, and the only global pharmaceutical company solely focused on this area. The company's products and development projects are primarily targeted at depression, schizophrenia, Parkinson's disease and Alzheimer's disease.

Unmet medical need in CNS
According to the World Health Organization, WHO, more than 700 million people live with psychiatric and neurological disorders globally. These are serious and life-threatening diseases that affect the quality of life of patients as well as of their relatives and caregivers. As these diseases also involve major socio-economic costs, it is imperative for society as a whole that new and innovative pharmaceuticals are developed. Over the past 70 years, a number of new treatments in CNS have emerged, but there remains a large unmet need for new and innovative therapeutics.

Call for a strengthened regulatory focus in CNS
Lundbeck finds that there is a strong case for taking an extra careful look at how regulatory advice, pathways and review frameworks can be adjusted to further support innovation and progress in treatment for brain diseases. Examples include allowing 'incremental' innovation benefits in areas of high unmet need and establishing better regulatory acceptance on addressing subpopulations.

Despite advances in research, brain diseases are lagging behind the other major disease areas such as diabetes and cancer. The latter have seen a leap in new treatment options, enabled in part by prioritized attention from decision makers, including regulators, providing support to innovation and ensuring that appropriate regulatory pathways have been tailored to suit treatment goals in relation to e.g. personalized medicines.

One notable exception to this is the approach taken towards advancing developing of new medicines for Alzheimer's Disease (AD), which could serve as inspiration for lifting regulatory focus in the broader field of CNS (2). This approach seems to be more commonplace in major disease areas. For example, in the area of oncology EMA have hosted in the past years multistakeholder workshops and strategy forums on topics including: "Site and Histology – Independent Indications in Oncology", "Challenges for the approval of anti-cancer immunotherapeutic drugs", "Health-Related Quality of Life in oncology", "single-arm trials in cancer drug evaluation" and "Paediatric oncology strategy workshop".

Due to the challenges in CNS medicines development we believe an "all hands-on deck"-approach with multistakeholder workshops and participation from other global decision makers, should be a priority in order to find a common path forward. A great example was the EMA workshop on the clinical investigation of medicines for the treatment of AD in 2014 and we hope to see a similar focus in other CNS areas as well, especially around topics such as outcome measures, transdiagnostic medicines development (across indications), long term value demonstration and paediatric medicines development.

A note on our response
Our response is in line with EFPIA's and thus we have filled in "rankings" on importance of the proposed recommendations similarly. Input complementing the aligned industry priorities from a CNS perspective can be found in the comment fields. Due to character limits we have submitted our full response via email to EMA.

(1) www.braincouncil.eu/VOTWP
(2) https://alzres.biomedcentral.com/articles/10.1186/s13195-016-0207-9

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.

Biomarkers and an integrated endpoint approach
Current regulatory emphasis on use of clinical outcome measures in medicines development for neurodegenerative diseases results in a need to run long term trials to detect a potential drug effect at the early and slowly progressing stages of the disease. This is not only extremely resource intensive, leading to companies moving away from such development programs, but also delays access to potential treatment to patients.

Key actions to propose:
• Due to the limitations of outcome measures in prodromal and pre-clinical phases of neurodegenerative diseases, Lundbeck advocates for global regulatory alignment on uses of for example integrated endpoint approaches, where combined data on several mutually supportive outcome measures can be interpreted as supporting efficacy as suggested for example in the draft FDA AD guidance (FDA, 2018)
• We also strongly support and encourage even more active EMA engagement in multi-stakeholder frameworks focused on endpoint development and usage to stimulate medicines development in brain diseases, such as for example the Critical Path for Parkinson's Consortium, as well as platforms for discussion such as the Alzheimer’s Association Research Roundtable

Scales and clinical meaningfulness
From a sponsor’s perspective, we have seen examples where clinician reported scales, previously considered golden standard in certain CNS indications, have been criticized by regulators for not being patient centric and that some items in the instrument construct are considered insensitive to detect change. In situations where no approved diagnostic or progression biomarkers exist and where there is uncertainty around previously accepted scales (ref rec 3.2.5), sponsors are facing a challenging situation in defining the primary endpoint.

Key actions to propose:
We would strongly encourage EMA to drive global multi-stakeholder discussion and alignment around CNS medicines development questions such as:
• What is needed to demonstrate measures (clinical scales) are meaningful to patients and fit-for-purpose in a clinical trial setting?
• How can we better address the significant but often overlooked unmet need of difficult-to-treat populations, e.g. via the use of retrospective data for patient inclusion when scientifically justified?
• How can the CNS field work collaboratively on ensuring that fit-for-purpose scores, including abbreviated or composite scores, are tested and validated for regulatory purposes?
• Conditions under which approval may be granted for treatment of a difficult-to-treat population without the need to demonstrate efficacy in the general population

Fostering patient focused medicines development
There is increasing acceptance of the relevance of patient and caregiver role in medicines development and regulatory decision-making (ref rec 3.3.3). We believe it would be highly relevant to discuss where and how insights like PROs, patient preferences and other types of patient input are considered relevant, reliable and meaningful in the overall B:R assessment, especially in CNS where the condition itself may interfere with the ability of the patient to self-report.

Key actions to propose:
An improved understanding of the EMA's forward-looking aspiration for including patient insights and experience data in regulatory reviews would enable more targeted investments in collecting such data for the benefit of public health. This is also a topic where alignment across decision makers including HTAs and payers is important, as suggested in the strategy, and where EMA, through its active collaboration with such decision makers, would have a prime opportunity to lead efforts globally.

Complex clinical trials and transdiagnostic medicines development
Within CNS, innovative clinical trial design, in particular basket trials, present an important opportunity to facilitate development of medicines for treatment of debilitating and often residual symptoms that manifest across diagnostic categories ("transdiagnostic drug development"). Examples of such symptoms include psychosis in schizophrenia and different types of dementia; and cognitive symptoms in depression, schizophrenia and primary cognitive disorders (e.g. AD). In addition, with the advancing scientific understanding of the underlying causes of CNS disorders, an emerging opportunity is to target a specific pathological hallmark that presents across different disorders.

While the recently published European "Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials" (CTFG, 2019) applies in principle accross diseases, the scope of the corresponding US guidance is limited to oncology (FDA, 2018), which represents a potential gap in global alignment.

Key actions to propose:
We encourage alignment between Agencies and welcome guidance that is broadly applicable across therapeutic areas, both in an exploratory and confirmatory context.

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.

Continuous regulatory advice along development continuum to accelerate access to CNS medicines

Lundbeck supports the EMA in its goal to provide continuous and integrated regulatory advice along the development continuum. Tools for this include PRIME (also covered under recommendation 3.1.3. “Promote and invest in the PRIME scheme”) and links to other facilitated regulatory pathways in their goal to accelerate access to CNS medicines. In order not to repeat EFPIA's points on need for alignment on advice across EMA Committees and EMA vs member state level, we will focus on the link to facilitated regulatory pathways.

Looking at statistics regarding facilitated regulatory pathway designations granted in Europe we can see that there have been for example all together 28 applications for PRIME designations in CNS medicines (3) (updated 29.5.2019), out of which only 7 were accepted - this could be due to several reasons but would merit further discussion on how to leverage tools like facilitated pathways to encourage innovation in CNS and especially psychiatry.

Lundbeck applauds the EMA for actively engaging with other Agencies to understand why and how each grant facilitated regulatory pathway designations and comparing the designations granted (for example under the remit of an EMA-FDA cluster). This promotes global alignment and understanding and for example according to recent numbers presented in public, when assessing common applications for both PRIME (EMA) and Breakthrough Therapy designation (FDA), two thirds of the decisions to grant or deny a designation were found to be the same across the two agencies. (4)

Where we do see a significant discrepancy in terms of agency approach is in relation to early regulatory approval (“conditional marketing authorization” in EU, “accelerated approval” in US, “accelerated approval with conditions” in Japan) - for example the use of progression biomarkers as primary endpoints for conditional marketing authorization is not explicitly supported in the EU whereas it is for accelerated approval in US. This also links to the use of integrated endpoint packages, as discussed earlier in our response.

Key actions to propose:
• Lundbeck urges regulators to align on acceptance of biomarkers and requirements for acceptance of integrated endpoint packages in relation to early regulatory approval
• Discussion on how facilitated regulatory pathways can be utilised to support and incentivise development of medicines for brain diseases, especially in psychiatry

(3) https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
(4) Kweder S (FDA): conference presentation titled “Breakthrough Therapy and PRIME - Exploring designation differences and similarities”, DIA Europe, Vienna 5.-7.2.2019

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.

A central issue to address future challenges for regulatory assessments is the role of non-randomized data on treatment effectiveness, and how evidence based on such data is considered in regulatory decision-making. The EMA strategy acknowledges that several of the strategic goals set out by EMA cannot be achieved through reliance on conventional trial designs. Additional types of data can potentially help inform B /R assessments and add more knowledge about relevance of the product to patients, prescribers and payers. It would be helpful to understand the Agency's thinking on the evolving role of non-randomized designs. What are the decision points for which evidence based on non-randomized data can be accepted? What criteria and standards should be applied to such evidence? Such alignment would facilitate building fit-for-purpose disease registries in brain disorders that could be leveraged for registrational studies as well as for follow-up of treatment effectiveness in routine care. For example, dementia registries exist in several European countries but have not to our knowledge been leveraged for regulatory purposes.
The US Food and Drug Administration has recently set out a framework for the use of real-world evidence (RWE) to inform regulatory decisions (5). Among other objectives the program aims to provide an empirical basis for the possibility to draw reliable causal inference based on observational data.

Key actions to propose:
• Further advance the global regulatory discussion on the place of non-randomised trial designs and data, with the aim of enabling more efficient medicines development without negatively impacting the foundation for B:R assessment
• Stimulate global regulatory leadership in building fit-for-purpose disease registries in brain disorders that could be leveraged for registrational studies as well as for follow-up of treatment effectiveness in routine care

Digital health technologies for data capture in clinical trials

Linking to recommendation 3.2.3 ("Develop the regulatory framework for emerging clinical data generation") the field of research and development in brain disorders will see an intensification of digital products used as biomarkers, tools for population stratification, outcome assessment as well as medicinal products.
Today, a plethora of digital health technologies (DHT) already exist on the market, but we need a better understanding of the applicability of these technologies in CNS development programs. Various technologies enable active as well as passive measures in a remote environment, allowing an innovative way to measure cognitive, functional and behavioral sub-domains in CNS clinical trials. For example, there is an opportunity to assess Parkinson's disease motor systems with DHT in clinical trials, where e.g. wearable sensor technologies could offer objective and un-obtrusive assessments in a home-environment. Also, early (prodromal) neurological disease stages may be difficult to differentiate solely on the basis of clinical observation, in which enhanced sensitive measures by DHT could be advantageous to identify subtle changes earlier.

Albeit promising, different DHT solutions need to be tailored to the specific disease as well as different stages of the disease. Moreover, demonstrated validity to use DHT to assess clinical outcomes in clinical trials in CNS is still lacking, and clear regulatory guidance is needed.

Key actions to propose:
• Further dialogue with regulators globally on how to utilise technology enabled objective assessment of cognition, behavior and functioning in CNS trials, as well as stakeholder alignment regarding privacy/GDPR considerations when utilising DHTs such as those meant for passive monitoring
• We support and encourage further EMA participation in multistakeholder efforts in this area, such as those conducted by the Critical Path for Parkinson's Consortium (CPP); Digital Drug Development (3DT) project which aims to obtain regulatory feedback on use of digital health technologies in Parkinson's disease clinical trials

(5) https://www.fda.gov/media/120060/download

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

Question 7 (human): The following is to allow more detailed feedback on prioritisation, which will also help shape the future application of resources. Your further input is therefore highly appreciated. Please choose for each row the option which most closely reflects your opinion. For areas outside your interest or experience, please leave blank.

Should you wish to comment on any of the core recommendations (and their underlying actions) there is an option to do so.

Strategic goal 1: Catalysing the integration of science and technology in medicines development (h)

	Very important	Important	Moderately important	Less important	Not important
1. Support developments in precision medicine, biomarkers and 'omics'	○	◉	○	○	○
2. Support translation of Advanced Therapy Medicinal Products cell, genes and tissue-based products into patient treatments	○	○	◉	○	○
3. Promote and invest in the Priority Medicines scheme (PRIME)	○	◉	○	○	○

4. Facilitate the implementation of novel manufacturing technologies	○	◉	○	○	○
5. Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	○	◉	○	○	○
6. Develop understanding of and regulatory response to nanotechnology and new materials' utilisation in pharmaceuticals	○	○	◉	○	○
7. Diversify and integrate the provision of regulatory advice along the development continuum	◉	○	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation** you are commenting on:

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

	Very important	Important	Moderately important	Less important	Not important
8. Leverage novel non-clinical models and 3Rs	○	○	◉	○	○
9. Foster innovation in clinical trials	◉	○	○	○	○
10. Develop the regulatory framework for emerging digital clinical data generation	○	◉	○	○	○

11. Expand benefit-risk assessment and communication	○	○	◉	○	○
12. Invest in special populations initiatives	○	◉	○	○	○
13. Optimise capabilities in modelling and simulation and extrapolation	○	◉	○	○	○
14. Exploit digital technology and artificial intelligence in decision-making	○	◉	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

13. Optimise capabilities in modelling and simulation and extrapolation (Recommendation 3.2.6.)

Specific for paediatric development Lundbeck would like to highlight the importance of advancing the recognition of extrapolation in a paediatric patient population in CNS. Extrapolation of evidence can minimise the number of children and adolescents included in clinical studies, especially exposed to placebo, and thereby reduce the overall study burden and maximise the information extracted from other sources without compromising the evidence base for any regulatory decision. As an example, demonstration of long-term efficacy is considered a relevant topic for extrapolation in a paediatric patient population.

Key actions to propose:
• Further the application of extrapolation in paediatric patient population where appropriate

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**:

15. Contribute to HTA's preparedness and downstream decision-making for innovative medicines (Recommendation 3.3.1)

Long term value demonstration and alignment with HTA bodies and payers

In line with the European Federation of Pharmaceutical Industries and Associations (EFPIA) response, Lundbeck welcomes the focus on joint clinical assessments and joint scientific consultations, which supports greater alignment on clinical evidence generation requirements and consequently swifter access to innovation for patients suffering from psychiatric and neurological disorders.

However, Lundbeck believes that due to specific features typically associated with brain disorders it is critical that a framework for evaluating long term value, specifically in CNS medicines, is developed and endorsed across stakeholders. Psychiatric and neurological disorders often lead to slow progressive functional loss, making it difficult to predict long-term outcomes from short-term clinical trials. Besides, the absence of biomarkers and the reliance on symptom scales makes it challenging to develop reliable models of long-term disease progression, leading to the question of acceptability of surrogate endpoints in clinical trials. In addition, the burden of brain disorders is mainly borne by actors outside of the health care system which implies that the value of innovative therapies will comprise improvements for informal caregivers, increased work productivity and other effects that are not systematically recognized by health care budget holders and decision makers. It is therefore of utmost importance that these aspects are well captured and evaluated via adequate methodologies and data sources including patient-centered outcomes and real-world data.

Key actions to propose:
Lundbeck encourages EMA to drive open dialogue with regulators, HTA bodies, payers and relevant stakeholders to align on acceptable ways to:
• Use disease modelling to support clinical relevance of treatment and long-term value demonstration in brain disorders
• Monitor patients long term in routine care in a cost-effective manner for value demonstration
• Leverage patient-reported outcomes in diseases where the disease itself may impair the ability of the patient to self-report, such as neurodegenerative diseases or schizophrenia
• Utilise new (digital) ways to measure functional outcomes

Also, in view of increasing alignment across regulators and HTA bodies and payers, in which Europe is taking the lead globally, Lundbeck believes a framework for evaluating long term value should be developed specifically for CNS.

Strategic goal 4: Addressing emerging health threats and availability/therapeutic challenges (h)

	Very important	Important	Moderately important	Less important	Not important
23. Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches	○	○	◉	○	○

24. Continue to support development of new antimicrobials and their alternatives	○	◉	○	○	○
25. Promote global cooperation to anticipate and address supply challenges	○	◉	○	○	○
26. Support innovative approaches to the development and post-authorisation monitoring of vaccines	○	◉	○	○	○
27. Support the development and implementation of a repurposing framework	○	○	○	◉	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Strategic goal 5: Enabling and leveraging research and innovation in regulatory science (h)

	Very important	Important	Moderately important	Less important	Not important
28. Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science	○	◉	○	○	○

29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions	○	○	◉	○	○
30. Identify and enable access to the best expertise across Europe and internationally	○	○	◉	○	○
31. Disseminate and share knowledge, expertise and innovation across the regulatory network and to its stakeholders	○	○	◉	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

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

Useful links

EMA website: Public consultation page (https://www.ema.europa.eu/en/regulatory-science-strategy-2025)

Background Documents

EMA Regulatory Science to 2025.pdf

Contact

RegulatoryScience2025@ema.europa.eu