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Public consultation on EMA Regulatory Science to 2025

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Introduction

The purpose of this public consultation is to seek views from EMA's stakeholders, partners and the general public on EMA's proposed strategy on Regulatory Science to 2025 and whether it meets stakeholders' needs. By highlighting where stakeholders see the need as greatest, you have the opportunity to jointly shape a vision for regulatory science that will in turn feed into the wider EU network strategy in the period 2020-25.

The views being sought on the proposed strategy refer both to the extent and nature of the broader strategic goals and core recommendations. We also seek your views on whether the specific underlying actions proposed are the most appropriate to achieve these goals.

The questionnaire will remain open until June 30, 2019. In case of any queries, please contact: RegulatoryScience2025@ema.europa.eu.

Completing the questionnaire

This questionnaire should be completed once you have read the draft strategy document. The survey is divided into two areas: proposals for human regulatory science and proposals for veterinary regulatory science. You are invited to complete the section which is most relevant to your area of interest or both areas as you prefer.

We thank you for taking the time to provide your input; your responses will help to shape and prioritise our future actions in the field of regulatory science.

Data Protection

By participating in this survey, your submission will be assessed by EMA. EMA collects and stores your personal data for the purpose of this survey and, in the interest of transparency, your submission will be made publicly available.
For more information about the processing of personal data by EMA, please read the privacy statement.

Questionnaire

Question 1: What stakeholder, partner or group do you represent:

- ○ Individual member of the public
- ○ Patient or Consumer Organisation
- ○ Healthcare professional organisation
- ○ Learned society
- ○ Farming and animal owner organisation
- ○ Academic researcher
- ○ Healthcare professional
- ○ Veterinarian
- ○ European research infrastructure
- ○ Research funder
- ○ Other scientific organisation
- ○ EU Regulatory partner / EU Institution
- ○ Health technology assessment body
- ◉ Payer
- ○ Pharmaceutical industry
- ○ Non-EU regulator / Non-EU regulatory body
- ○ Other

Name of organisation (if applicable):

European Social Insurance Platform

Question 2: Which part of the proposed strategy document are you commenting upon:

- (●) Human
- ( ) Veterinary
- ( ) Both

Question 3 (human): What are your overall views about the strategy proposed in EMA's Regulatory Science to 2025?

Please note you will be asked to comment on the core recommendations and underlying actions in the subsequent questions.

The Strategic Reflection includes many important objectives for the EMA. Nevertheless, there is room for improvement.
The proposed strategy lacks a definition of key priorities but rather loses itself in detail. These details are primarily driven by a firm belief in technology and the advancement of science and thereby neglect the prioritisation and definition of medical objectives and public health needs. Nevertheless, with regards to healthcare, technologies and scientific developments do not present a value in themselves.
EMA states that its mission is the protection of human health. The paper seems to be focused (almost exclusively) on ways to bring new products to patients as fast as possible, implicitly assuming that all new products have an added benefit for patients and/or health systems. The paper lacks a proper reflection of harms and risks. Indicative is the fact that – in contrast to the veterinary part of the paper – pharmacovigilance is only mentioned once in the paper. EMA seems to consider itself as a co-developer of medicinal products. This is a slippery slope as it may endanger EMA's independence as regulator responsible for ensuring safe and effective medicines. Speedy access must not come without proper evidence defining a new product's place in therapy and ensuring that its benefits outweigh its risks.
In addition, many new products have no or a very limited added benefit but nevertheless come with extremely high price tags that put health systems under strain. Rather than contributing to a higher level of health protection - the contrary is true – it endangers current levels access.
The Strategic Reflection also lacks a critical reflection on the need for better quality clinical trials (e.g. randomisation).
Several reflections provided rely a lot on the feasibility of Big Data and so-called Real World Data (RWD). Observational data, which is the preferable term for RWD, has always had its place in medical sciences. Many projects in the fields of pharmacovigilance and healthcare research rely on observational data. Nevertheless, observational data is inherently prone to bias. Thus, instead of promoting the use of observational data for all research questions, one should first define questions that need to be answered and then select the type of data that is suited best to answer it.
The Strategic Reflection conveys the idea that Big Data and precision medicine will be widely operational in the period leading up to 2025. The potential impact of new data generated throughout the life-cycle should be critically discussed (e.g. re-assessments, withdrawal of marketing authorisation, safety alerts, changes in SmPCs).
The current strategy would appear to extend the role of EMA far beyond that of marketing authorisation decisions and its regulatory competencies to, for example, biosimilar uptake, drug shortages, and data generation for down-stream decisions. However, EMA's role in these processes must be limited to information sharing and facilitating better cooperation between the different stakeholders, including payers and HTA bodies, without impinging on their respective competencies.

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)

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

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.

HTA is the basis for evidence guided reimbursement decisions. Thus, EMA should aim to ensure that requirements for HTA processes are already integrated in the pre-authorisation phase. Trial designs should reflect the requirements of HTA assessments.
Whenever it is considered impossible to present sufficient evidence of added patient benefit at the time of approval, EMA should cooperate with HTA on how to address open questions post-authorisation.

Second choice (h)

16. Bridge from evaluation to access through collaboration with Payers

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.

Difficulties in obtaining reimbursement are mentioned as a factor for delayed or no market access, necessitating better interaction of EMA and payers. While we welcome this concept generally, it has to be made clear that patients often do not have access due to the industry's global pricing strategies where products are either not or only with a huge delay placed on the markets of poorer and smaller countries or excessive price expectations hinder reimbursement. "Difficulties in obtaining reimbursement" translates to health systems not being able to justify spending of large parts of finite health system resources in order to finance therapies that have not conclusively proven their added beneficial effects. Therefore, increased collaboration between the regulator EMA and the payer community, as well as other public health actors, is of vital importance.
Many of the proposed actions concern areas with unmet medical need. This concept has to be clearly defined in collaboration with all stakeholders. A better description of the eligible patient population and the underlying rationale are of utmost importance for payers and will improve EMA's labelling.

Third choice (h)

11. Expand benefit-risk assessment and communication

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 more systematic application of the benefit-risk assessment methodology is highly welcomed, especially an improved communication with payers and HTAs on suitable comparators, therapeutic context and outcomes.

When patient preferences are increasingly incorporated it has to be ensured that this is done in a methodologically sound, transparent and impartial way with clear rules for conflict of interest.

Regarding communication, EMA should publicly explain its decisions and also provide insights into the benefit-risk balance, especially warning against possible harm so that patients are informed about side effects.

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

A critical evaluation:
- of EMA's current methods and potential adaptations (e.g. risk assessment/pharmacovigilance, conditional marketing authorisation, withdrawing market authorisation, orphan drug designation etc.).
- of EMA's actual role: "co-developing" medicinal products and health technologies and the assessment of added value should not be part of EMA's remit.
- concerning questions of transparency such as availability and access to data submitted by the marketing authorisation holder to the agency, including individual patient data that could be made accessible to independent researchers.
- of EMA's possible role in guaranteeing market launch in all European markets, for example by implementing a "medicines tracker" to follow up if and when centrally authorised products are actually launched throughout Europe and mitigate or at least increase awareness of "strategic launch sequencing".

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:

General comment:

EMA should clarify that:
a) support of developments in precision medicine, biomarkers and 'omics',
b) translation of ATMPs into patient treatments,
c) promotion and investing in the PRIME scheme
are only useful, if these developments are targeted at high unmet medical needs and have the potential to substantially improve the health status of patients. Central marketing authorisation for "me-too" products can lead to improved competition (as we have seen with the new generation medicinal products for Hepatitis C), but products which do not offer a real benefit should not profit from incentives aimed at tackling high unmet medical need. We call for a more critical approach and greater transparency.
While EMA needs to expand expertise to critically assess and evaluate new technological developments such as ATMPs, EMA's role – above all – is to ensure that only products with sufficient and appropriate data demonstrating their safety and efficacy reach European patients. Its role should not be driving innovation, but rather the critical evaluation of potential advancements for patients.
Regarding facilitating new manufacturing technologies, we agree that this is useful if it is linked to higher quality of the product and/or greater efficiency of the process.
We believe it is very important that EMA develops appropriate regulatory pathways for products associated with medical devices, in-vitro diagnostics and borderline products and strategies to deal with nanotechnologies and new materials in pharmaceuticals (as far as these products will be relevant by 2025).

Conclusion: the paper fails to focus sufficiently on the products that address high unmet medical need and that truly warrant regulatory support.

Specific comments:
1.
Validation of endpoints based on biomarkers has to be done prior to market authorisation and is the responsibility of the applicant.

Only biomarkers, that have been proven to select a subpopulation that benefits significantly more from a treatment than other patient populations or that are directly related to clinically relevant changes in patient relevant outcomes are acceptable.

EMA should develop and provide a detailed protocol for biomarker validation to be employed by applicants

2 and 3.
In these processes the emphasis needs to be on high unmet medical need which needs to be defined. This definition needs to take into account the public health perspective.
The integration of evidence that fulfils the needs of HTA and payers in the development programmes is very important and necessitates the development of a clear structured participation of these stakeholders.
EMA needs to develop methods for an impartial and transparent participation of all stakeholders involved

throughout the life-cycle.

In addition, the Agency needs to develop appropriate mechanisms for re-evaluation as well as withdrawing marketing authorisation when products do not live up to their expectations in the long run.

3.
PRIME relies on the appointment of a dedicated rapporteur for each product. This bears the risk of bias as pointed out in the European Ombudsman's enquiry into scientific advice by EMA.
Faster marketing authorisation often leads to a greater reliance of post-marketing evidence generation, resulting in a risk shift to patients and healthcare systems. PRIME has to be limited to selected cases of high unmet medical need, which are clearly defined by stakeholders in advance, and SMEs, which lack capacities for regulatory issues. Outcomes of PRIME need to be closely monitored to see if it fulfils its goal of accelerating market access while improving available evidence.
We do not consider that the promotion of PRIME is necessary.

4-6
We support the concept that regulatory models need to be reviewed with view to novel manufacturing technologies, medical devices and borderline products as well as new materials, but this should not result in reduced standards of quality, efficacy and safety. Protection of public health remains paramount.

7.
Recalling the recent European Ombudsman enquiry into scientific advice provided by EMA, while consistent advice throughout the development continuum is desirable, some flexibility needs to be preserved to react to new developments and to avoid potential bias.

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**:

General comment:

Importantly, EMA should maintain the requirement for high levels of evidence of efficacy and safety obtained from clinical trials (preferably RCTs) for all products where possible. This must be part of EMA's strategic goals.

However, increasingly technological developments and manufacturers are driving the development of new products aimed at small patient groups. This leads to a growing number of new products with limited evidence on efficacy and safety at the time of marketing authorisation. Therefore, collaborative evidence generation is needed. The focus should be on the best ways of generating Real World Evidence (RWE) by randomised studies, based on real world data (RWD). It must be clarified which data are appropriate to answer which questions.

Providing HTA and payers with better evidence is key for the future handling of those products. However, all participating parties need to be aware of the different duties and questions each stakeholder has to answer and respect these responsibilities.

Specific comments:
8.
The 3R principles are established but hard to implement. Their use should be further optimised, but the limits of non-clinical models should be respected. Although they do have their role in pre-clinical development, their value in clinical development is limited.

9.
Many so-called modern trial designs still suffer from methodological problems that result in high susceptibility to bias. Thus, currently they should be considered acceptable for explorative trials only. Surrogate endpoints present problems as discussed above, for biomarkers. As long as they have not been validated for predicting patient relevant outcomes, their use for establishing a positive benefit-harm ratio cannot be recommended.

10.
Before developing methodologies to incorporate big data, it should be made clear under which circumstances, for which products (pharmaceuticals, in vitro diagnostics, borderline products) and for which purposes this kind of data can and will be used in regulatory decisions.
Quality standards have to be defined to incorporate such data into regulatory decision-making as indicated by the HMA-EMA Joint Big Data Taskforce.
Data protection and data ownership need to be clarified.
Potential advantages of new data sources should be investigated e.g. novel methods of self-measurements by patients in clinical trials, since they can be supportive, as long as they represent patient relevant outcomes.
11.

Improved communication concerning the benefit-risk assessment is strongly supported. While it has to be clarified that HTA/payers and regulators have different responsibilities and methodological standards, understanding the reasons for regulatory decisions is key to HTA and downstream decision-making. Remaining uncertainties should also be described in more detail than currently.
Regarding patient preferences, methodological caveats have to be taken into account – preference studies are often misleading, as preferences change with experience of the disease, are less precise with increasing complexity of decisions and tend not to elucidate the whole picture.

12. / 13.
Earlier access to populations in urgent need should not be a standalone aim without taking due account of efficacy/effectiveness and safety. Adaptive approaches with iterative development imply a risk shift from pre- to post-market, resulting in larger populations at risk rather than risk minimisation.
Supplementing clinical trial data with clinical care data is valuable, but it does not replace the need for clinical trials. Modelling and simulation should not apply to ALL products. Such models, as applied to paediatric populations, already demonstrate their limitations. Their extension to other areas, including biosimilar development, is difficult to justify and needs to be corroborated with significant evidence. It should be specified when these approaches will be used, in particular when they should replace clinical trials.

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**:

General comment:

Payers welcome EMA's cooperation with HTA institutions, regulators and manufacturers in early dialogues on products that have a potentially high impact on the health status of patients. This dialogue should be early, and it must be clarified how HTA data requirements and post-market evidence generation will be integral to obtaining market authorisation.
Reinforcing patient relevance in evidence generation is indeed an important objective.

So far, the possible use-cases for Big Data/RWD are more promise than fact and should be reflected in a more balanced way. The limitations of Big Data/RWD in terms of validity and utility in comparison to existing evidence standards have to be clearly addressed and a discussion about when and for what purposes this kind of data can be used has to take place. Thus, clear guidelines and transparent requirements need to steer these developments.

Payers welcome the support of EMA concerning availability and uptake of biosimilars.

Trust in the EU regulatory system will improve if EMA takes a more critical stand regarding studies of manufacturers (e.g. demanding relevant comparators, validated surrogate outcomes …) and the expected benefits.

Specific comments:
15. We welcome EMA's intention to continue to work closely with healthcare systems. Although differences exist in the way HTA and EMA examine new medicines, these differences are justified and do not hinder better cooperation. However, the differences should be better explained in the public domain.
The incorporation of evidence needed by payers and HTA into development plans is indispensable. HTA and regulators have different responsibilities and therefore ask different questions.
When monitoring the impact of decision-maker engagement, target parameters should be defined. While discussion often focusses on access alone, in reality, the triangle of access, affordability and added benefit is relevant.
We ask for clarification of what "contributing to HTA priority setting" implies.

16.
Healthcare systems are organised on a national level and have developed differently therefore different payment models are valid. Nevertheless, a single platform for dialogue, focusing on evidence generation plans is welcomed.

17.
When enhancing patient involvement, potential conflicts of interest need to be addressed. We support the focus on patient reported outcomes, but we need to establish a common understanding between patients and HTA and payers. In this respect, the value of commonly used quality-of-life questionnaires needs to be reviewed.

18. / 19.
RWD would be better described as observational data. Using this term provides a more precise description of the underlying data and does not imply that interventional data (e.g. from RCT) do not reflect reality.

RWD should not be promoted, rather it should be emphasised that RCTs are still the gold-standard for demonstrating efficacy. RWD can provide additional information but it is more suited to the post-authorisation phase. It should be clear when and why RWD will be used in a product's life cycle. Standardisation, data quality, registration in publicly accessible databases, reproducibility, validated statistical analyses and transparency regarding conflicts of interest have to be ensured.

Data protection and ownership need to be clarified.

20.
Product information, including the SmPC and package leaflet, needs to be improved. Some smaller markets with less common languages may benefit from a higher number of generics, if product information is supplied electronically. However, the concept of a real-time product information raises problems in terms of adaptability and consistency of these legal documents.
Importantly, the paper form of the package leaflet has to remain available to ensure that also digitally-naïve patients can access the information provided.

21.
As payers we support the goal of promoting the availability and uptake of biosimilars as they are important for reducing costs for medicinal products without endangering patients' care. Communication to this effect needs to be strengthened. EMA has a role to play in this. Guidelines on the exchangeability of biosimilars would be appreciated.

22.
Trust and confidence in the EU regulatory system needs to be strengthened. Trust is built on reliability and transparency. The over-use of fast track approvals, which increases uncertainty, has already undermined the trust of many stakeholders. This needs to be rectified.

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**:

General comment:

Payers welcome the engagement of the EMA in emerging health threats (including AMR) as well as improving the availability of pharmaceuticals addressing these needs. Nonetheless, increasing manufacturing capacity in Europe and new business models are not seen as part of EMA's tasks, but require a political mandate. Still, fostering new approaches for the development and approval of vaccines is a welcomed objective. However, instead of "influencing vaccine decisions", EMA has a more appropriate role in "promoting scientific information about vaccines"
Repurposing is a promising field for further support, and we welcome the ongoing discussions in the STAMP on a possible repurposing framework. However, repurposed drugs lead to new intellectual property rights and inappropriately higher prices, endangering accessibility – also for those patients using the drug for the existing indication.

Specific comments:
23.
We support the aim of implementing health threat plans and refining preparedness approaches.

24./ 26.
While the development of new antimicrobial agents is extremely important. However, neither business models nor vaccination decisions are remits of EMA.

25.
It remains unclear, how regulatory decisions may influence the location and extent of manufacturing capacities, or manufacturing issues leading to shortages. More information would be desirable.

27. Repurposing is a promising field for further support. The development of a suitable framework to support the repurposing of medicinal products is a topic of ongoing discussions within STAMP.

Importantly, we need to avoid that the repurposed drugs lead to new intellectual property rights and therefore to higher prices – also for those patients using the drug for the current disease.

Any changes to the current legislation deemed necessary should not lead to different standards for repurposing and applications for extensions of indications under the usual regulatory path.

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**:

General comment:

Identifying solutions to current and future regulatory needs and challenges is fundamental to EMA's work. It needs to underpin the whole regulatory strategy rather than being one strategic goal. In order to address the regulatory challenges, EMA needs to be active in scientific networks and interact with academia.

Thus, it would be more appropriate to add a separate "methods" chapter where it is explicitly stated how strategic goals 1-4 will be achieved.

Concerning these research activities, EMA should further ensure complete transparency in all stakeholder involvement.

Specific comments:
28.
It is unclear what is meant with “funders”, national research centers, payers, commercial parties?
Health care professionals, payers and patients should be involved. Under all circumstances, transparency has to be ensured in all research collaborations and conflict of interest needs to be addressed.

Academia could also play an important role in defining novel clinical trial designs and developing methods to enable adequate analyses of data obtained

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