EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05/03/2019
EMA/158095/2019
Human Medicines Research and Development Support

European Medicines Agency process for engaging in externally funded regulatory sciences and process improvement research activities for public and animal health

Table of Contents

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

1. Executive summary

This document sets out criteria that should be followed when considering Agency engagement in externally funded regulatory science[1] activities to support regulatory decision-making for the benefit of public and animal health. To this end it highlights the existing possibilities to interact with EMA and provides a framework for dealing with third party requests and/or proposals for participation in regulatory science activities. It discusses a number of points to consider – in line with relevant EMA procedures - when deciding on the Agency's participation in regulatory science projects. It also defines possible roles and levels of active involvement to increase clarity about potential implications for the Agency and its staff. The document furthermore sets out a centralised process to channel all requests and/or proposals for regulatory science activities through senior Agency management.

In summary, when deciding on an EMA involvement in regulatory science activities, the following questions need to be addressed:

- what are the anticipated resource implications? (a specified number of days of scientific staff and administrative staff over a specified number of years)

- how does the project fit with the EMA Network strategy, mission, and tasks according to the EMA founding regulation?

- what is the anticipated involvement of EMA Committees and Working Parties?

- what is the anticipated collaboration with external stakeholders?

- what is the anticipated impact for the EMA and for EU public health?

- what is the risk of (perceived) conflict of interest?

- are existing, routine, opportunities for regulatory interaction being used optimally? (could the consortium be sufficiently supported by a combination of innovation task force, SME office and scientific advice, for example?)

It should be understood that EMA engagement in an externally funded Regulatory Science activity does not imply that the EMA endorses and/or will be bound by the project outcome(s).

2. Introduction

In order to comply with the Agency's mission *to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health* it is important for the Agency to be aware of the latest scientific knowledge and methodologies and to actively support science in relevant areas, as defined in the EU Medicines Agencies Network Strategy [2] and the EMA work programmes. This is further emphasised in the recently published strategic reflection on EMA Regulatory Science to 2025 [3].

Notwithstanding the above, the Agency needs to carefully consider its mandate, priorities, and use of resources. A number of opportunities for interacting with EMA on matters related to medicines research

[1] Regulatory science is defined as a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools.
[2] EU Medicines Agencies Network Strategy to 2020 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500185138.pdf
[3] https://www.ema.europa.eu/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

and development already exist and should be explored before requesting direct EMA engagement in a project; these are referred to in section 5 of this document and they are briefly described in the Agency's SME user guide.

This document is an update of EMA/573402/2017 to take into account the revised EMA founding regulation. It also takes into account lessons learnt from past, ongoing collaborations, and the need to make best use of the Agency's resources.

2.1. Current involvement of the Agency in regulatory science activities

Over the years the Agency has progressively intensified its interactions with stakeholders beyond the regulatory network, including a dialogue with pharmaceutical industry as well as increasing the involvement of patients, consumers and healthcare professionals in the Agency's work. The Agency is also making ongoing efforts to engage to a greater extent with academia, learned societies and research groups, as reflected – for example - in the establishment of the Academia Framework, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). As a result of this engagement and the importance placed on regulatory sciences to support its business processes, the Agency is receiving an increasing number of requests to contribute to research.

The Agency's involvement in regulatory science to date includes:

- organising scientific workshops with participation of various stakeholders,
- participating in scientific conferences,
- providing experts to external/scientific/regulatory advisory boards of regulatory science projects and boards of learned societies, including development of scientific guidelines,
- establishing and supporting networks of excellence e.g. in paediatric (Enpr-EMA) and in pharmacoepidemiology (ENCePP) research,
- cooperating with academic networks, such as the ACCELERATE platform on paediatric oncology
- engaging in regulatory science initiatives of other European or international health bodies [including the European Centre for Disease Prevention and Control (ECDC), the World Health Organisation (WHO), FDA, etc.],
- performing literature reviews and database studies in relation to medicines evaluation,
- analysing in-house data (e.g. across products and/or indications) and publishing the results to contribute to better drug development and/or further improve the evaluation and supervision of medicines. In-house or internal data refers to historical data stored in internal databases, for example on scientific opinions/recommendations of the various EMA committees and working parties, such as CHMP, PDCO, COMP, Scientific Advice, etc.,
- advising on policies[4] and identifying regulatory science priorities for public (or part public) funding programmes [European Commission (EC) Directorate General for Research & Innovation and its research programmes, as well as contributing to the Innovative Medicines Initiative (IMI) Scientific Committee],
- launching in-house initiatives on topics of interest in relation to regulatory science,

[4] E.g. Art 4(2)(b) of Orphan Reg 141/2000

- commissioning, coordinating or actively participating in externally funded and/or led scientific projects,
- providing for visiting academics, for example as seconded national experts or as placements to trainees funded under the Marie Skłodowska-Curie Actions.

3. Scope

This document mainly addresses externally funded regulatory science collaborations (focusing on human or veterinary medicines) involving contribution from or led by external parties. Major in-house initiatives (potentially including involvement from the European Medicines Regulatory Network, the Agency's Scientific Committees and Working Parties) should also follow relevant parts of this process. The process excludes projects addressed in the Agency's *policy on training and career development* (Doc. Ref. EMA/68023/2011) and which have been approved in accordance with the staff Regulations Part I, Title II, Art 12.

4. Objectives

The document:

- Provides guidance surrounding the decision on the involvement of the Agency in externally funded regulatory science activities,
- Defines possible roles and levels of involvement of EMA in externally funded regulatory science activities,
- Sets out a harmonised and centrally coordinated approach to oversee and manage EMA participation,
- Provides guidance on if and when participation in regulatory science activities may constitute a conflict of interest for EMA, to be read in conjunction with existing internal documents and guidelines, and
- Identifies other relevant points to consider, providing consistency and a common framework for making decisions on the Agency's involvement in externally funded regulatory science activities.

5. Various levels of involvement of EMA

Absence of a legal basis for becoming involved, as well as resource and financial limitations, often make it difficult to justify direct EMA participation in externally funded regulatory science projects. Therefore, before seeking EMA participation in a project, researchers are encouraged to consider the inclusion of a 'regulatory interaction' stream or work package, as appropriate, in their grant proposal. For this, please explore using as much as possible the existing routes for interaction with EMA or national regulators. Routes available at EMA include:

- the SME office
- the Innovation Task Force (ITF)
- Qualification of new methodologies
- Scientific Advice and Protocol Assistance

- Paediatric Investigation Plans
- Orphan Designations

In some cases however, different interaction with EMA may still be required, for example when data held by EMA are to be used (e.g. Eudravigilance), when EMA needs to benefit from hands-on experience in the area of work covered by the project, or where direct EMA participation is deemed key to the success of the project, thus increasing the efficiency of public spending. Occasionally, advisory roles might be considered for projects where there is a clear need for Agency input on regulatory aspects and close liaison is considered of value by the Agency.

When considering participation in an externally funded regulatory science project, the most suitable level of EMA involvement should be identified taking into account the Agency's mission and the expected benefits for the Agency, its wider network and EU public health, resource constraints and potential (actual and/or perceived) conflicts of interest. It is also important to clarify the expectations from the involvement of EMA vis-à-vis what the Agency realistically will or can contribute. This should particularly cover the understanding that such involvement does not imply the EMA endorses and/or will be bound by the project outcome(s).

In cases where 'routine' interaction with regulators is deemed insufficient for a research project (by the project coordinators and the EMA), the Agency's level of involvement in a project may range from taking on an advisory role to being a project lead.

5.1. Advisory role

EMA might agree to join an advisory board of a project, reviewing the research agenda and project progress and providing expert regulatory guidance. Situations where this might be appropriate include where the project has an important public health impact or where the project provides significant opportunities for capacity building (for example, the establishment of scientific or methodological infrastructure or frameworks, networks, etc).

EMA staff will not sign a confidentiality undertaking with research consortia and the responsibilities of the advisory role should be agreed a priori in writing with EMA. The presence of an EMA staff member in an advisory board does not circumvent the correct use of existing EMA procedures and channels of interaction (i.e. ITF, Qualification and Scientific Advice, Protocol Assistance and Paediatric Investigation Plans).

From a resource perspective, membership of an advisory board may consist of offering feedback on results and other project documents, as well as participation in meetings. The required resources and time commitment are normally limited.

5.2. Consortium partner

Occasionally, EMA may agree to become consortium partner. When EMA is consortium partner, it has rights and obligations under the terms of the respective project or grant agreement, as applicable. The actual contribution, timelines and other conditions of participation are laid down in the agreements or annexes thereof and hence there is a clear understanding regarding the commitments made by EMA in terms of resources and project deliverables to be provided.

5.3. Coordinator of a regulatory science project

Exceptionally, EMA may agree to take the role of the overall scientific project coordinator. Coordination of regulatory science projects usually requires substantial resources and depending on the timelines of

the project, a commitment as coordinator might last several years. Given that leading on research is not the Agency's core business, and given that the Agency cannot be reimbursed for the activity, this is not a commitment EMA takes on lightly.

6. Resources and financial implications

Active participation in regulatory science programmes can be resource-intensive and might involve a commitment over several years, which presents a challenge in terms of sustainability. Taking into account Article 7 of the EMA Financial Regulation, the Agency is permitted to receive research grants. In addition, for activities where EMA does not receive a research grant, EMA can still receive reimbursement of travel, accommodation and subsistence costs.

Whilst certain services to provide research and development support are established by the Agency, engagement in research projects is not necessarily part of its core business. Hence there is a need to ensure strategic, effective use of resources in this area..

7. Area of regulatory science

The Agency's scientific activities will focus on certain areas of regulatory science taking into account

- the applicability and relevance to strategic aims of the Agency, and in particular to that of its Committees,
- the added value of contribution from regulators to the project, and
- the need for continuing and strengthening inter-institutional and international collaborations e.g. with WHO, ECDC, FDA, EC, PMDA, EFSA, Health Canada.

7.1. Applicability and relevance to the Agency's strategy

Areas of regulatory science to which the Agency might contribute must be closely related to the Agency's role and responsibilities and aligned with its strategic priorities, as defined in the EU Medicines Agencies Network Strategy[5] and EMA's Single Programming Document[6].

The EU Medicines Agencies Network Strategy to 2020 has identified the following four strategic themes:

1. Contributing to human health
2. Contributing to animal health and human health in relation to veterinary medicines
3. Optimising the operation of the EU regulatory network
4. Contributing to the global regulatory environment

The Agency might also support regulatory science projects expected to improve how the Agency and its Committees evaluate and supervise medicines. Projects should already foresee and subsequently measure the impact of the research in the evaluation and supervision of medicines, for the benefit of public and animal health.

EMA will not get involved in activities that are outside its legal role or its mission statement.

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500185138.pdf
[6] EMA Work Programmes (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000242.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac058002933c).

7.2. Added value of contribution from (and to) regulators to the project

The support of projects will depend on the added value of contributions from regulators. Projects that may benefit from the involvement of more "hands on" regulatory expertise include research into the development of methodologies and capacity building in regulatory sciences.

Some projects may already collaborate with national competent authorities thereby covering the need for regulatory input. However, in some cases it might still be important for the Agency to be involved, e.g. to uphold EU interests. Furthermore, active involvement from EMA in externally funded regulatory science activities may be critical to support their relevance to regulatory decision-making and to ensuring they improve business processes for the benefit of public and animal health.

EMA's interest in a regulatory science project will also take into consideration the potential benefits to the EU regulatory network, such as improved awareness of developing areas of science and opportunities to influence strategic regulatory science agenda setting (e.g. some of the EU COST initiatives).

8. Other points to consider

Other points to consider for the Agency's involvement in regulatory science activities include:

- Quality and soundness of the regulatory science proposal,
- Confidentiality and access to data,
- Potential impact on regulatory practice, and
- Conflicts of interest.

8.1. Quality and soundness of the regulatory science proposal

As a rule, the Agency will only contribute to projects that have been successfully assessed by a scientific or award committee and which are expected to improve the innovation, evaluation, supervision and positive public health impact of medicines. Regardless, situations may still occur where the research proposal does not meet Agency standards for example regarding transparency, research independence, or ethical aspects. Projects should be compliant with applicable legal and ethical obligations and follow relevant good practices.

8.2. Confidentiality, access to data and disclosure of results

The Agency has access to a unique repository of both non-clinical and clinical data on numerous medicines which represents an extremely valuable source for drug-related regulatory science. The Agency will make available its data as openly as possible whilst ensuring protection of personal data and commercially confidential information in line with the applicable legislation, the Agency's Publication of clinical data policy[7], Regulation (EC) No 1049/2001 and the related policies[8], and existing confidentiality arrangements with our international regulatory partners.

It is assumed that external requests for EMA to participate in - or advise on - a regulatory science project are motivated by EMA's unique role as central EU regulator and its resulting capacity to

[7] Publication of clinical data policy
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp .
[8] Access to documents
http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/document_listing/document_listing_000312.jsp&

mobilise and provide expertise, as well as a pan European regulatory perspective. In order to fulfil its role, EMA should be able to report to/discuss with its committees and working parties on any aspect of a regulatory science project. This will be done in consultation with the project leader and/or steering group and respecting intellectual property rights and confidentiality considerations, in order not to compromise subsequent publication in scientific journals.

It is expected that all results will ultimately be communicated to external stakeholders in a transparent way, whether by means of publication in a medical journal or on the Agency's website.

EMA is subject to the provisions of Regulation (EU) 2018/1725on the protection of personal data. The involvement of EMA in regulatory science projects should be compatible with its obligations as Data Controller, in particular in light of the interpretation provided by the European Data Protection Supervisor regarding the allocation of responsibilities in case of scientific regulatory science projects in which EMA participates.[9]

8.3. Expected impact on regulatory practice

An assessment of the expected impact of the project outputs on regulatory practice may be performed at an early stage of the evaluation, including a review of the opportunities and constraints linked to such potential implementation, such as impact on public health, feasibility and resource implication. Such assessment may also help identify those projects that have the greatest impact in a context of prioritisation of resource allocation.

8.4. Conflicts of interest

The Agency demands high standards of professional conduct, integrity and independence in any activity it engages in. Management of Conflicts of Interest is thus of paramount importance. The potential for a conflict of interest to arise from a regulatory science activity should be established in line with the *EMA Code of Conduct*[10]*, the Decision on rules relating to Articles 11a and 13 of the Staff Regulations concerning the handling of declared interest of employees of the EMA* and the related *Implementing rules relating to Articles 11a and 13 of the Staff Regulations* concerning the handling of declared interests of employees of the European Medicines Agency (EMA/565945/2009).

Conflicts of interest are related to the role and level of involvement of the Agency. EMA will only contribute to projects where there are no significant Conflicts of Interest - either because they do not exist or because they can be managed appropriately. Conflicts of interest will be reviewed by a panel independent from the persons engaged in project support and, where feasible, will involve at least one expert member external to the Agency.

Type and scope of regulatory science activities

In some cases, the subject of the work itself could create a conflict of interest, e.g. work that will lead to the development of a particular medicinal product or that will only benefit one or a few companies. Furthermore, careful evaluation is required when considering direct involvement in projects seeking to develop methods for drug development which at a later stage may become part of scientific advice or a marketing authorisation application, and as such be assessed by the Agency. However, work that is

[9] https://secure.edps.europa.eu/EDPSWEB/webdav/shared/Documents/Supervision/Priorchecks/Consultations/2011/11-03-21_EMA_EN.pdf
[10] The European Medicines Agency Code of Conduct (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/wrapper_page.jsp&mid=WC0b01ac0580029338#).

non-competitive in nature and does not overlap with regulatory decision-making will be less likely to create conflicting interests.

Therefore, study protocols and work programmes will be reviewed for elements that could give rise to concerns regarding the Agency's impartiality in medicines evaluation, including the motivation behind the proposed work as well as the intended outcome.

Regulatory science involving cooperation with industry

In general terms, EMA will not engage in regulatory science activities with pharmaceutical companies unless these are conducted within an official public private partnership, e.g. the Innovative Medicines Initiative (IMI). In any case, the Agency will preserve its (financial) independence throughout the process (see also explanations above in relation to 'type and scope of regulatory science activities') and all relevant aspects of the interaction between the Agency and industry should be clearly defined, preferably as part of a written cooperation agreement.

Joint activities of regulators and pharmaceutical industry are very sensitive and have the potential to create a negative perception with the general public. Therefore, even in the absence of established conflicts of interest, the Agency will always apply a proactive approach and communicate in a clear and transparent manner on all relevant activities, addressing potential concerns in the perception of the Agency's actions.

Collaborative regulatory science involving participation from non-industry parties

While less apparent than in the case of pharmaceutical companies, interaction with universities, EU or non-EU National Competent Authorities, other non-industry based institutions, or learned societies may also require careful consideration as these parties may themselves hold interests (e.g. receipt of private grants or collaboration with industry) that could be in conflict with the Agency's role and responsibilities. Appropriate consideration will be given to such interests, if any.

Grants and remuneration of EMA activities

The Agency may be involved in (and potentially lead) projects that receive grants from public and private sources. As of 28 January 2019, the Agency can sign grant agreements with the European Commission.

Publications by Agency staff

Agency staff may be involved in publications arising from their contribution to project work. This might include publications alongside authors from pharmaceutical companies taking into account all other considerations as described above. All publications should be approved by the peer review group and prepared in line with the *Policy on scientific publications by EMEA staff*[11], the *Policy on scientific publication and representation for European Medicines Agency's scientific committees and their members* [12] and should be consistent with the Agency's general position as well as previous communications or decisions, and be compliant with relevant rules and principles of the Agency.

[11] European Medicines Agency Policy for Scientific Publications by EMEA Staff (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/04/WC500089594.pdf).

[12] Policy on scientific publication and representation for European Medicines Agency's scientific committees and their members (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004627.pdf)

9. Procedure for deciding on EMA involvement

EMA has a strategic and proactive approach to regulatory science. The Agency carefully considers its involvement in regulatory science projects in line with its established priorities and agreed work programme(s) and is, therefore, highly unlikely to engage in any regulatory science activity which does not fall within this scope.

The following procedure should be followed before engaging in any new regulatory science activity or extending existing work.

a) **Requesting EMA involvement -** Proposals suggesting the initiation of a project or asking for EMA's collaboration in a project originate from individuals or institutions external to the Agency and should be channeled through the Science and Innovation Support office (SIS) office regulatory.science@ema.europa.eu. They may also come from any EMA staff member, from any member of a Scientific Committee or Working Party, or from external EMA experts. These should also involve the SIS office.

   So as to ensure a 'level playing field', EMA will not commit to contributing to research consortia during the competitive stage of a grant application. EMA will only agree to formally collaborate with a consortium once the initial selection has taken place and a winning consortium has been chosen. Consequently, the Agency will also not provide letters of support to grant proposals during the competitive stage of a grant application.

   After the evaluation phase, the coordinators of successful EC-funded proposals for which funding is available, are invited to start preparations for the grant agreement; they receive the evaluation result letter and the Grant Agreement Preparation (GAP) Invitation Letter. The GAP Invitation Letter sets the deadlines for the first submission of grant data & annexes, for the signature of the declarations of honour by all members of the Consortium, as well as the deadline for grant signature.

b) To ensure the above deadlines can be met, consortia who wish for EMA to contribute to the project as a consortium partner should contact EMA about this as soon as the GAP invitation letter is received. **Consideration of Agency involvement** - In the first instance, SIS office will liaise with the relevant operational sector and triage all proposals based on the following questions:

   - what are the anticipated resource implications? (a specified number of days of scientific staff and administrative staff over a specified number of years)

   - how does the project fit with the EMA Network strategy?

   - what is the anticipated involvement of EMA Committees and Working Parties?

   - what is the anticipated collaboration with external stakeholders?

   - what is the anticipated impact for the EMA and for EU public health?

   - what is the risk of (perceived) conflict of interest?

   - are existing, routine, opportunities for regulatory interaction being used optimally? (could the consortium be sufficiently supported by a combination of innovation task force, SME office and scientific advice, for example?)

   The above analysis will be discussed with EMA management.

c) **Outcome** - SIS will inform the concerned parties of the EMA position. If the decision is to contribute to a project, SIS office will coordinate the initial contact with the funding body and the

requestor, and will provide administrative support. This includes interaction with the consortium regarding the consortium agreement and the grant agreement. As a matter of principle, if the Agency is represented on the advisory board of research consortia, it will not sign non-disclosure agreements. For consortium partnerships, the Agency will adhere to the ENCePP code of conduct.