EUROPEAN MEDICINES AGENCY
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Data Analytics and Methods

Technical specifications for open invitation to tender

Procurement procedure "Quality, efficacy and safety studies on medicines", reference no. EMA/2020/46/TDA

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Technical specifications for open invitation to tender

No. EMA/2020/46/TDA – Quality, efficacy and safety studies on medicines

1. Title of the invitation to tender

This document contains the technical specifications for the open invitation to tender no. EMA/2020/46/TDA for quality, efficacy and safety studies on medicines.

2. Purpose and context of the invitation to tender

The European Medicines Agency ("the Agency" or "EMA") is a decentralised agency of the European Union (EU) based in the Zuidas area of Amsterdam.

EMA's mission is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

EMA:

- Supports medicines development by giving scientific advice and providing guidance to developers of medicines;
- carries out scientific evaluations of medicines for human and veterinary use that are the basis of the European Commission's decision on whether a medicine can be authorised for marketing throughout the EU;
- monitors the safety of medicines in the EU throughout their lifespan; and
- provides information on medicines to healthcare professionals and patients.

EMA is responsible for the centralised procedure for the authorisation of medicines for human and veterinary use resulting in a single evaluation and a single authorisation for the whole of the EU. The centralised procedure is compulsory for certain medicines, including human medicines intended for the treatment of HIV/AIDS, cancer, diabetes or neurodegenerative diseases, designated orphan medicines intended for the treatment of rare diseases, and medicines derived from genes, cells, tissue-engineering and biotechnology processes.

For veterinary medicines, the centralised procedures is compulsory for:

- medicines developed by either recombinant DNA technology or controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma and monoclonal antibody methods,
- veterinary medicines intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals,
- veterinary medicines containing new active substance,
- biological veterinary medicinal products which contain or consist of engineered allogeneic tissues or stem-cells and novel therapy veterinary medicinal products.

EMA coordinates the work of around 4,500 experts made available by the EU Member States. These experts evaluate the medicines and are members of the Agency's scientific committees, its working parties and groups.

The Agency's recommendations on medicines are based on rigorous scientific standards and the available evidence. Pharmaceutical companies applying for a marketing authorisation for a medicine have to submit comprehensive data on the safety, efficacy and quality of their medicine. These data are scrutinised by the Agency's experts, who will recommend the marketing authorisation of a medicine if the data convincingly show that its benefits outweigh its risks.

EMA is a scientific body. Decisions on whether to grant, suspend or revoke a marketing authorisation for centrally authorised medicines are issued by the European Commission, based on the Agency's scientific opinions. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU and EEA-EFTA States (Iceland, Liechtenstein and Norway). This allows the marketing authorisation holder to market the medicine and make it available to patients and healthcare professionals throughout the EEA.

The Agency is responsible for coordinating the EU's pharmacovigilance system for medicines. It constantly monitors the benefit-risk balance of medicines through the EU network and can take action if information indicates that the balance of a medicine has changed since it was authorised. The Agency also monitors the subsequent effectiveness of actions taken and the impact of relevant legislation.

The purpose of this procurement is to purchase the services of research organisations to perform pre- and post- authorisation quality, efficacy and safety research to generate data and information to support regulatory decision-making in the human and veterinary medicines regulatory domain.

3. Subject of the tender

3.1. Context

The benefit-risk balance of a medicinal product at the time of its initial marketing authorisation is based on evidence generated by a clinical development programme. Appropriate risk management systems are adopted to ensure the safe and effective use of the medicine post-authorisation. Building knowledge throughout the lifecycle of a medicinal product is therefore critical in fully characterising the safety and effectiveness profile of a medicine and thus its benefit-risk balance while it is marketed.

While valid scientific evidence generated by an MAH remains at the core of regulatory evaluation, additional and relevant data and information available from alternative sources or new data may be generated to further inform regulatory decision-making. Technological and scientific developments of recent years provide unprecedented opportunities to further support regulatory decisions based on the best available scientific evidence.

The EMA needs to have access to data sources and scientific expertise in selecting and using methods appropriate to a wide range of quality, efficacy and safety questions and in understanding the evidence needed for regulatory decision making.

3.2. Technical specifications

The Agency considers that it may require the services of research organisations to perform pre- and post- authorisation quality, efficacy and safety research to generate data and information to support regulatory decision-making in the human and veterinary medicines regulatory domain. Research topics are those with high public and animal health relevance and with a European impact. The

scope of the funding covers both nationally and centrally authorised products, including vaccines. The results obtained from this research will subsequently be assessed by the responsible Agency Committee(s) regarding the need for regulatory action and any further research.

To conduct this research the Agency as a first step seeks to put in place through this procurement procedure multiple framework contracts with a maximum of 10 research organisations per Lot, for a period of four years each. Framework contractors will subsequently be invited to submit tenders for specific studies on topics identified by the Agency in collaboration with its Scientific Committees as part of the scientific evaluation of the benefit-risk profile of authorised medicinal products.

The specific studies may concern research under Lots 1 to 6 (as described in detail in section 3.3.); tenderers may apply for one or several Lot(s):

- Lot 1: Pre-clinical research
- Lot 2: Veterinary studies
- Lot 3: Statistical research
- Lot 4: Qualitative research
- Lot 5: Pharmacoepidemiological research
- Lot 6: Quality of medicines

To help provide an understanding of their ability to perform the type of research described in the Lot(s) they apply for, the tenderers should provide information on expertise and experience relevant to this type of research (see also section 15. Selection criteria: technical and professional capacity). The tenderers are not expected to have all the required expertise or data sets 'in house' or in one location. However, the tenderers are expected to have access to a network of scientists where one or more elements of the expertise described are available as needed (see also sections 4.2. Subcontracting and 4.3. Joint offers).

3.3. Lot and service descriptions

Lot	Description
Lot 1: **Pre-clinical research**	This Lot concerns research using in vitro, in vivo and in silico models (including method and model development) to address relevant scientific or regulatory questions in the context of the development and use of human and veterinary medicinal products including specific regulatory requirements, such as the evaluation of maximum residue limits (MRLs) for food producing animals. The studies that can be procured in this Lot may use literature sources or they may generate new in vitro or in vivo experimental data (e.g. laboratory trials), apply in silico tools or use non-mammalian in vivo assays to perform the following evaluations: • to evaluate formation of metabolites and their potential toxicity, • to predict the potential mutagenicity and carcinogenicity in humans of impurities or active substances through structure activity relationship analysis, • to detect potential hazards to embryo-fetal or postnatal development,

Lot	Description
	• to evaluate on-/off-target effects of medicines including advanced therapeutic approaches such as stem cells and gene editing, • to review susceptibility data for antimicrobial or antiparasitic substances and assess the effect of microbial interaction on resistance development, • to evaluate indications, target species or populations, • to evaluate bioequivalence or effective dose, • to assess the validity of defined biomarkers or models. Contractors may be required to perform non-clinical studies using a broad range of methods for answering a wide range of regulatory questions, including gathering toxicological information for safety assessment. Comprehensive availability of validated and regulatory accepted in vitro, in vivo and in silico models will guarantee the efficient use of these methodologies to support the regulatory decision-making process. EMA supports the implementation of the so-called 3Rs principles - replace, reduce and refine - for the ethical use of animals in medicine testing across the European Union (EU) with the aim of encouraging alternatives method to the use of animals in the testing of medicines when generating data, information and evidences for the medicines risk/benefits evaluation. This Lot therefore also requires expertise in support of 3Rs approaches and knowledge on qualified alternative in vitro, ex vivo, and non-mammalian in vivo assays to detect potential hazards and understand mechanism of toxicity and reproductive toxicity. Contractors need to have knowledge and access to integrated data infrastructure and innovative computational methods and tools which could support the human translational safety assessment, as well as expertise in specific veterinary areas and domains such as (but not limited to) antimicrobial resistance, antiparasitic resistance, environmental risk assessment, safety and residues studies relevant to consumer safety for veterinary medicines. The ability and expertise to establish specific models may be required as well as established systems ensuring adequate data quality (e.g. according to GLP principles).
Lot 2: **Veterinary studies**	This Lot addresses research (excluding experimental and pre-clinical research) related to the development and use of veterinary medicinal products (VMPs) in companion and farm animals and the associated hazards for public health, animal health or the environment. The contractors may be asked to perform a broad range of retrospective studies, based on secondary analysis of available data sets (database studies), and also to conduct prospective studies using data which are accessible or can be collected via established network(s) or infrastructures. The studies that may be required include (but are not limited to): 1. Identification, compilation and characterisation of data sources, in

Lot	Description
	order to establish an inventory of real world data and metadata (e.g. ecotoxicological data, wildlife population data, data on antiparasitic and antimicrobial resistance, data from devices collecting data on companion and farm animals, use of VMPs) pertaining to various veterinary areas: 1.1. provision of scientifically valid evidence to support regulatory decision-making, 1.2. support for the development of predictive models for the identification of emerging health threats (e.g. new antimicrobial resistance mechanisms), 1.3. experience on the use of statistical power analysis and the enabling of sustainable, efficient and coordinated regulatory actions and information dissemination in the area of environmental risk, animal and public health, 1.4. enabling of a better understanding of the association of antimicrobial use or sales in animals with antimicrobial resistance development, in a 'One Health' context (integrating animal, human and environment data) by linking data on the veterinary antimicrobial use or sales volume to other data sources (e.g. electronic health records, patient level prescribing data, real world data, literature, metadata, antimicrobial resistance data and human medicines data); 1.5. development of interpretative criteria for antimicrobial susceptibility and the establishment of clinical breakpoints by linking data on dosing regimens with antimicrobial susceptibility data (e.g. minimal inhibitory concentrations) and clinical efficacy of antimicrobials in target bacterial species. Continuous rolling review of the available data sources is envisaged based on an annual review and update of the aforementioned inventory. 2. Conduct of prospective and retrospective observational studies (including development of infrastructures for continuous data collection) on risks and efficacy or effectiveness, regulatory outcomes, and measures taken to identify, characterise and anticipate future trends, and to identify adequate regulatory actions in the area of (i) safety (e.g. environmental risks assessment, antimicrobial resistance risk assessment, target animal safety and consumer safety assessment) and (ii) efficacy or effectiveness (e.g. for the evaluation of VMPs intended for use in minor species or limited markets). Observational studies may include the development of infrastructures for data collection of antimicrobial use in companion animal population that enable interrogation and hypothesis generation of the impact of different prescribing practices (e.g.

Lot	Description
	dosing regime, treatment duration, route of administration) in the development of antimicrobial or antiparasitic resistance and the consequences for animal and public health. 3. Analysis of regulatory and non-regulatory information on efficacy and safety data (including but not limited to environmental toxicological data, veterinary farm management systems data and pharmacovigilance data) for: 3.1. the overall efficacy and safety characterisation and profiling of veterinary medicines authorised or under development in the EU; 3.2. identifying unmet medical needs; 3.3. the evaluation of the effectiveness of regulatory measures established by EMA and other regulators; 3.4. identifying future trends and derive adequate regulatory actions in the area of veterinary medicines regulation, animal and public health and risk management; 3.5. identifying socio-economic and ethical considerations relevant to the decision making on regulatory actions for medicines used in companion and food producing animals; 3.6. identify the impact of veterinary antimicrobial use on antimicrobial residues and their persistence in the environment, as well as on the development of resistance bacteria and resistance genes in the environment and the associated animal and public health consequences. 4. Analysis of regulatory outcomes related to efficacy and safety of veterinary medicines from other international regulatory authorities to evaluate EU regulatory actions and support the evolution and design of new coordinated veterinary regulatory processes (e.g. in the context of VICH and Codex Alimentarius, including JECFA). 5. Exploration of the feasibility to establish the required infrastructures and to implement pilots for cost- and resource-effective, prospective, controlled studies in farm animals using commercial farm management systems; enabling better understanding on exposure and/or effects of veterinary medicines or in order to collect relevant data on animal health. 6. Performance of rapid descriptive studies aimed at providing data to facilitate key decision-making process in the context of crisis situation (e.g. pharmacovigilance issues, emerging or zoonotic diseases). 7. Addressing questions that may need to be answered very rapidly (i.e. within a few weeks), e.g. in relation to the extent of VMP usage or numbers of cases of a suspected adverse reactions within

Lot	Description
	a defined indication or time window following exposure to a VMP. In this context, Lot 2 also concerns, but is not limited to, studies providing a rapid descriptive analysis based on (all) data sources available across different EU Member States. These data sources should in particular include data providing information on use, efficacy and safety of VMPs in companion and farm animals. In order to deliver the required study and analysis results, the contractors will need to have relevant and substantial expertise and experience in one or more areas as specified above. Furthermore, the contractors will need to have access to required data sources, depending on the area of expertise and experience, such as (i) data on companion animals derived from veterinary practitioners (e.g. SAVSNET); (ii) data on farm animals derived from commercial farm management systems or (iii) appropriate expertise and capacities to collect required data for instance by conducting prospective epidemiological studies.
Lot 3: **Statistical research**	This Lot addresses statistical research for human and veterinary medicines. The studies that can be procured in this Lot may include (but are not limited to): • studies aiming to foster innovation in clinical trials, e.g., on new and emerging endpoints or innovative clinical trial designs such as platform or in silico trials; • studies aiming to develop new or to compare existing statistical analysis methods, e.g. for time-to-event endpoints; • studies on the use of extrapolation of treatment effect from one population to another, or modelling and simulation (model-informed drug development) to address regulatory questions, including, for veterinary studies, extrapolation of treatment effects across animal populations and species and model informed studies for residue depletion (e.g. physiologically based pharmacokinetic modelling); • studies aiming to support the implementation or the development of regulatory guidelines on methodological aspects, e.g., the ICH E9(R1) addendum; • statistical analyses, predictive analyses and visualisation of raw data (including clinical trial data) aiming to identify future health emerging risks and support regulatory decision making. Most studies may require the contractors to study the properties of the statistical methods under investigation, e.g. by simulation or by using real datasets of human or animal populations. For this purpose, the contractors should have access to datasets from a variety of sources: clinical trials, observational studies, electronic health records or other real-world veterinary data sources (e.g. farm data management systems, data on wildlife population, ecotoxicological and environmental data).

Lot	Description
Lot 4: **Qualitative research**	This Lot addresses research providing qualitative information about prescribing and use patterns of medicines, the cognitive processes and experiences of patients and healthcare professionals, such as knowledge, risk awareness, trust, reasoning processes and attitudes about medicines, the communication needs and the experiences of using medicines and applying risk minimisation measures in real life. Qualitative research may also investigate options and impact of engagement of stakeholders, in particular patient and healthcare professional representatives and their organisations, e.g. how stakeholders get involved by regulatory bodies, how their input shapes regulatory decisions, how far expectations and needs are met, and how information from regulatory bodies is perceived, disseminated, used and trusted. Qualitative research may require multiple methodological approaches with different theoretical origins and tools. Methods are described in Good Pharmacovigilance Practices (GVP) Module XVI.Add.II.3.1 (under public consultation). Contractors require expertise in use of specific methods for qualitative research, for example: • Theories such as action research and case studies (potential for a mixed-methods approach), ethnography/netnography (for studying social interactions, behaviours and perceptions within groups, organisations and communities), phenomenology (for studying an individual's lived experience of events), and grounded theory (for generating new theories regarding social phenomena). • Qualitative data generation from focus groups and in-depth interviews, including sampling strategies. • Qualitative data analysis using deductive and inductive approaches such as content analysis, discourse analysis, thematic analysis, grounded theory and triangulation of data.
Lot 5: **Pharmaco-epidemiological research**	This Lot addresses a variety of non-interventional studies measuring the utilisation and effects of medicinal products used in accordance with normal clinical practice in the human population. This Lot may therefore address topics related to drug utilisation, safety and effectiveness of medicines, including vaccines. Studies of this Lot may include (but are not limited to): • descriptive studies, aiming, for example, to estimate the prevalence, incidence or characteristics of exposures or health outcomes in defined time periods and population groups; • etiological studies measuring the strength and determinants of association between an exposure and the occurrence of a health outcome in a defined population taking into account sources of bias, potential confounding factors, including time-varying factors, and effect modifiers; these studies may include those conducted to obtain a better understanding of hazards associated with medicine use during pregnancy and/or breastfeeding; • studies estimating the impact of a regulatory intervention (such as the

Lot	Description
	effectiveness of risk minimisation measures) on drug utilisation or health outcomes, considering both the intended and unintended consequences of the intervention; methods for these studies are described in the Good pharmacovigilance practices (GVP) Module XVI revision 3 and its Addendum II (under public consultation); • pharmacogenomics studies aiming at the investigation of safety or effectiveness; • systematic reviews and meta-analyses consisting in the identification, integration and critical appraisal of evidence on the use, safety and effectiveness of medicines; • methodological research to improve methods and operational implementation (e.g. validation of data sources and data models) of the above-mentioned studies, including methods of signal detection from spontaneous reports or other data sources. Some questions raised by the EMA and its scientific committees may need to be answered rapidly to allow fast decision-making, especially in relation to descriptive, etiological and impact studies. The timelines for such studies may be short and will be determined by the research question, e.g. delivery of the study results within a few weeks or months after the contract is signed. Rapid studies require readiness in terms of e.g. organisation, procedures and protocols in place, fast access to databases, analytical pipelines or use of a common data model allowing rapid statistical analyses. On occasions, the questions addressed via a specific study might aim to inform the design or to supplement the results of randomised controlled clinical trials of efficacy. The contractors should therefore have an understanding of such trials. For descriptive, etiological and impact studies, access to at least three data sources in different EU Member States is required. The contractor will have access to data via in-house access, remote accessor upon agreements already in place or planned to be established with data owners or third parties. The processes in place for data validation and data quality control is documented and available (e.g. via the database holder's website or other published information). Contractors may use innovative methods or tools such as harmonised coding systems and/or common data models. Contractors may also be required to perform studies with primary data collection. To demonstrate their ability to perform observational studies on medicines used in pregnancy or breastfeeding, contractors should have access to data sources such as disease registries or electronic health records where pregnancy information, pregnancy outcome data and pregnancy exposure information can be available, including delayed or long-term pregnancy outcomes.
Lot 6: **Quality of**	This Lot may address (but is not necessarily limited to) three types of research: i) studies to investigate the origin of harmful impurities in medicines, ii) studies aiming to develop understanding of, and regulatory

Lot	Description
medicines	response to, nanotechnology and new materials in medicinal products and iii) studies to evaluate the potential impact on the quality of veterinary medicinal products when administered via drinking water to farm animals due to the different water qualities used across the EU. The studies may require the combination of different types of expertise. i) Sometimes, safety issues arise with medicinal products due either to inherent properties of the active substance, impurities introduced through its synthesis, or via other components. These safety issues are often associated with the toxic effects of such impurities or degradants and trigger regulatory intervention, i.e. quality defect or referral procedures. For products that have been on the market for many years, development took place at a time when scientific understanding was less developed and analytical technology was less sensitive and potentially unable to detect and identify trace impurities. In order to understand the impact on patients, animals and consumers of foodstuffs of animal origin, prevent further exposure, and to inform regulator and market actions, it is vital to understand the origin of these impurities or degradants. Manufacturers and marketing authorisation holders responsible for these products may be unable to conduct adequate investigations in a timely manner, providing only hypothetical root causes without conclusive evidence. In such cases, the regulatory decision making would benefit from additional supportive data. Contracting these studies to external laboratories would allow timely generation of independent data to allow more informed regulatory decisions. Understanding the origin of harmful impurities and degradants in medicinal products for human and veterinary use requires expertise in organic chemistry and related disciplines encompassing the following skills: • Synthetic chemistry – the ability to rapidly manufacture compounds of interest; • Root cause analysis; • Physical organic techniques such as isotopic labelling experiments and potentially, the ability to conduct follow up in vivo pharmacokinetic studies; • Expertise in elucidating the mechanism of chemical reactions; • Specialised analytical expertise and access to analytical equipment able to follow chemical reactions (solution and solid phase) in real time such spectroscopic instruments (NMR, IR, UV) containing flow cells, variable temperature (and cryo) probes. ii) To develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals is a goal of the EMA Regulatory Science Strategy to 2025. Despite the numerous scientific publications in this field, there is a gap between basic research and the translation of these products into clinic. Further studies are required to further characterize these materials/drug delivery systems and understand the fundamental science of how these materials interact with biological systems. The service requested

Lot	Description
	therefore encompasses both primary laboratory research and the pooling of existing literature information covering the following aspects: • development and standardisation of analytical/testing methods related to the quality characterization of nanomedicines and new materials; • understanding of the critical quality attributes (CQA) of a given new material/ nanomedicine (e.g. particle size and size distribution, zeta potential) and the relationship between those and the biological activity and in-vivo behaviour of the product (PK/PD)), in both human and animal patients. iii) Water quality varies across the EU and, for veterinary medicinal products administered via drinking water to farm animals, there could be a need to consider how this might impact on the quality and, therefore, the efficacy of the products. Differences in parameters such as hardness (Ca2+, Mg2+ and other ions), biocides and pH, might have an effect on quality characteristics and stability of VMPs, e.g. degradation of the active substance, decrease in solubility causing precipitation, formation of complexes, which can result in lower doses than those intended to be taken by the animals. There are published studies performed with antibiotics indicating that these differences in qualities of water have an impact on the stability of veterinary medicinal products, but there can be other active substances, including other antimicrobials, affected.

3.4. Support from the European Medicines Agency

For specific studies, the Agency will provide the successful contractor(s) with access to the information required to perform the studies, including, where applicable, an updated assessment on the medicinal product issue that is the subject of the research.

For Lots 3 (Statistical research), 4 (Qualitative research) and 5 (Pharmacoepidemiological research) the Agency recommends the conduct of this research in line with the principles and tools for scientific independence, transparency and sound methods of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP[1]) and requires registration of studies in the EU PAS Register[2].

3.5. Minimum requirements to be met by the tender

The following minimum requirements must be met by the tender for it to be considered compliant with the technical specifications. Tenderers must provide a completed declaration which can be found in **Annex IV**. Failure to confirm compliance with all the following requirements shall result in elimination from the procurement procedure.

The minimum requirements shall be observed throughout the entire duration of the contract. Compliance with these requirements is mandatory and cannot be subject to any assumptions, limitations, conditions, or reservations on the part of a tenderer.

[1] http://www.encepp.eu/index.shtml
[2] http://www.encepp.eu/encepp_studies/indexRegister.shtml

Minimum requirements applicable to all Lots:

- Compliance with applicable environmental, social and labour law obligations established by Union law, national legislation, collective agreements or the international environmental, social and labour conventions listed in Annex X to Directive 2014/24/EU.
- The working language of the Agency is English and the contractor must confirm that it will be able to communicate with the Agency in English for seamless implementation and execution of all the services covered within the scope of the contract, including responsibilities resulting from regulatory requirements such as Health and Safety and Data Protection, as well as for the efficient and timely response in respect to contract management.
- Processing of personal data in connection with this service must comply with EU data protection legislation, in particular, Regulation (EU) 2016/679 (General Data Protection Regulation), in such a manner that processing of personal data will meet the requirements of Regulation (EU) 2018/1725.

Minimum requirement applicable to Lot 5 in addition to above:

- Access to at least three relevant data sources in different EU Member States - via in-house access, remote access or agreements in place with data owners or third parties - is required to perform studies on the utilisation, safety or effectiveness of medicinal products. This access should be documented via e.g. publications, agreement document or statement from database holders.

3.6. Place of performance

The services will be performed at the contractor's premises. On occasion, the contractor may be requested to attend meetings for the purpose of presenting research findings to relevant scientific committees, working parties or advisory groups. These meetings may take place virtually or at the EMA premises.

4. Participation in the tender

4.1. Agreements on public procurement

Participation in procurement procedures is open on equal terms to all natural and legal persons falling within the scope of the Treaties. This includes all legal entities registered in the EU and all natural persons having their domicile in the EU. Participation is also open to all natural and legal persons registered or having their domicile in a non-EU country which has an agreement with the European Union in the field of public procurement on the conditions laid down in that agreement. The rules of access to the market do not apply to subcontractors.

The procurement procedures of the Agency however are not open to tenderers from countries which have ratified the Multilateral Agreement on Government Procurement ("GPA")[3].

4.2. Subcontracting

Subcontracting is the situation where the contractor enters into legal commitments with other economic operators which will perform part of the contract on its behalf. The contractor retains full liability towards EMA for performance of the contract as a whole.

[3] This includes the United Kingdom.

All contractual tasks may be subcontracted unless the technical specifications expressly reserve the execution of certain critical tasks to the sole tenderer itself, or in case of a joint tender, to a member of the group.

If the tenderer envisages subcontracting any part of this contract, **Annex V** should be completed indicating clearly the identity, roles, activities and responsibilities of subcontractor(s) and specifying the volume/proportion for each subcontractor.

Attached to the completed **Annex V** should be a signed letter of intent by each subcontractor stating its unambiguous undertaking to collaborate with the tenderer if it wins the contract and the extent of the resources that it will put at the tenderer's disposal for the performance of the contract.

A completed **Annex III** is required by all identified subcontractors. Tenderers should note their obligation to replace a subcontractor if it is in an exclusion situation or does not meet a specific selection criterion.

If such documents are not provided, the Agency shall assume that the tenderer does not intend subcontracting.

Subcontracting to subcontractors identified in a tender that was accepted by EMA and resulted in a signed contract, is considered authorised. Any consequent change in subcontracting is subject to prior approval by EMA.

Supplementary information on subcontracting:

- The same legal entity may participate simultaneously as a group member for one lot, and as a subcontractor for another lot.
- Subcontracting of one and the same legal entity in more than one lot is acceptable.
- There is no limit to the volume/proportion of the tender being subcontracted.

4.3. Joint offers

Joint offers are permitted.

A joint offer is a situation where a tender is submitted by a group (with or without legal form) of economic operators regardless of the link they have between them. The group as a whole is considered the tenderer.

All members of the group assume joint and several liability towards EMA for the performance of the contract as a whole.

Group members must appoint a Group leader and a single point of contact authorised to act on their behalf in connection with the submission of the tender and all relevant questions, clarification requests, notifications, etc., that may be received during the evaluation, award and until the contract signature. The model cover letter for tenderers in **Annex Ia** must be used.

In case of a joint offer, an overview should be provided indicating clearly the identity, roles, activities and responsibilities of each individual partner.

Supplementary information on joint offers:

- The principle of 'one tender per tenderer' applies. It therefore follows that the same legal entity may not participate as a group member in more than one tender for the same lot (e.g. two different departments from the same academic institution would be considered the same legal entity).

- The group members are required to nominate a lead representative who is empowered to submit the tender on behalf of all partners and to act as the main contact point for the Agency (see also: cover letter in Annex 1a).

4.4. Identification of the tenderers

The tender must include a cover letter drafted using the appropriate template provided in **Annexes Ia and Ib** to this document. The cover letter must present the name of the tenderer (including group leader and all members of the tendering group in case of a joint tender) and identified subcontractors if applicable, and the contact information of the single contact person in relation to this tender.

In case of a sole tenderer, the cover letter must be signed by the person(s) empowered to represent the tenderer and entitled to sign the contract in case the offer is successful.

In case of a joint tender, the cover letter must be signed by (a) duly authorised representative(s) for each member of the tendering group, and an overview should be provided indicating clearly the identity, roles, activities and responsibilities of each individual partner.

For sole tenderers and joint tenders where the composition remains unchanged in all lots tendered for: only one cover letter is required, regardless of the number of lots tendered.

For joint tenders where the composition of the consortium is different per lot: a separate cover letter is required for each lot tendered.

5. Additional documentation available to tenderers

Further information about the work of the Agency can be obtained on its website: http://www.ema.europa.eu.

Further information about the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) can be obtained on its website: http://www.encepp.eu

6. Site visit

Not applicable.

7. Variants

Not applicable.

8. Estimated contract volume

Without this being binding, the Agency estimates that up to four specific studies may be required per lot per year. Typically, the budget per study may be approximately €60,000 to €500,000. On occasion the Agency may increase this budget depending on the topic and complexity of the research.

The maximum budget foreseen for all six lots over four years, without this being binding, is €33,000,000.

The framework contract value per lot over the contract duration of four years is estimated as follows:

Lot no.	Description	Contract value (in EURO)
1	Pre-clinical research	€ 3,000,000
2	Veterinary studies	€ 3,000,000
3	Statistical research	€ 3,000,000
4	Qualitative research	€ 2,000,000
5	Pharmacoepidemiological research	€ 19,000,000
6	Quality of medicines	€ 3,000,000

The Agency may exercise the option to increase the contract financial ceiling at a later stage via negotiated procedure for the repetition of similar services in accordance with Article 11.1(e) of Annex I to Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union. This procedure may only take place at the latest during the three years following contract signature and shall be triggered by the need to increase the financial ceiling up to a maximum of 50% of the initial ceiling.

9. Price

9.1. Currency of tender

Prices should be submitted in Euro. The costing sheets attached to these specifications must be used to submit a financial tender – **Annex II.1-6**.

Tenderers must provide the price requested and not propose any different pricing structure.

It is the responsibility of each tenderer to ensure that the total amount of the tender inserted in the eSubmission field "Total amount" corresponds to the amount indicated in the uploaded financial offer. In case of discrepancies, only the amount indicated in the financial offer will be taken into account.

9.2. All-inclusive prices

Prices submitted in response to this tender must be inclusive of all costs involved in providing the services as described in the hypothetical specific service assignment or 'case study' in section 17.1. (e.g. to include travel, subsistence). No expenses incurred in the performance of the services will be reimbursed separately by the Agency.

9.3. Price revision

Not applicable.

9.4. Costs involved in preparing and submitting a tender

The Agency will not reimburse any costs incurred in the preparation and submission of a tender. Any such costs must be paid by the tenderer.

9.5. Period of validity of the tender

Tenderers must confirm as part of their declaration in **Annex Ia or Ib** that the tender (including prices) is valid for nine months from the closing date for receipt of tenders.

9.6. Protocol on the Privileges and Immunities of the European Union

The Agency is, as a rule, exempt from all taxes and duties, and in certain circumstances is entitled to a refund for indirect tax incurred such as value added tax (VAT), pursuant to the provisions of Articles 3 and 4 of the Protocol on the Privileges and Immunities of the European Union. Tenderers must therefore give prices which are exclusive of any taxes and duties and must indicate the amount of VAT separately.

10. Payment arrangements

In accordance with the contract, payments shall be made in arrears following receipt of an invoice and completion of services. A detailed payment schedule will be provided for each individual specific contract. Payments are linked to the formal acceptance of individual deliverables by the Agency and will be effected upon reaching certain milestones (e.g. acceptance of study protocol, acceptance of study report).

Payments shall be made within 60 days of receipt of the request for payment and shall be deemed to have been made on the date on which they are debited to the Agency's account. The Agency may, however, after giving notice to the tenderer, defer payment if the products or services covered by the request for payment are contested by the Agency.

All invoices shall be sent in PDF format to the following e-mail address: ema.vendorinvoices@ema.europa.eu.

The Agency shall be bound to comply with payment periods only if requests for payment are properly presented at the above address.

The tenderer is required to give the following information on all invoices:

- The breakdown of fees for services, the contract price and the amount of VAT applied, if any, or, whenever appropriate, a note that the services rendered under the contract are exempted from VAT in accordance with the national tax law by which the tenderer is governed.
- A reference to the contract number and specific contract number.
- A reference to the Agency's purchase order number which shall be communicated from time to time.

The successful contractor, to which a specific contract is awarded following a re-opening of competition, will be requested to establish a list of all pre-existing rights and rights of creators and third parties on the results of this specific contract or parts thereof. This list must be provided no later than the date of delivery of the final study results. The Agency will provide a form for this purpose which must be attached to any interim or final invoice.

11. Contractual details

A draft contract is attached to these Technical Specifications as **Annex VI.** Tenderers must confirm acceptance of the draft contract and terms and conditions of the tender as part of their tender response and as part of their declaration in **Annex Ia or Ib**.

Important information applicable to Lots 3, 4 and 5 (Statistical research, Qualitative research and Pharmacoepidemiological research):
Tenderers' attention is drawn to the fact that the ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies will be an integral part of, and shall prevail over, the framework contract.

The Agency wishes to conclude a maximum of 10 framework contracts for each lot to provide services, as and when required, for a period of four years. A framework contract will establish the terms governing specific contracts to be awarded during a given period.

A framework contract shall be awarded to the first 10 ranked tenders per lot, which comply with the minimum requirements specified in the procurement documents and are submitted by tenderers with access to procurement, not in an exclusion situation and fulfilling the selection criteria.

Whilst the Agency wishes to conclude up to 10 framework contracts per lot, the very minimum number of framework contracts will usually be three per lot. This is to ensure genuine competition during the lifetime of the framework contracts.

If there is only one acceptable tender per lot, the procedure for this particular lot will be cancelled.

Multiple framework contracts with reopening of competition are implemented through specific contracts for which all contractors under the same lot are invited to compete. Specific contracts shall be awarded on the basis of reopening of competition for each study. A specific contract shall be awarded to the contractor who has submitted the most economically advantageous specific tender on the basis of the same or, if necessary, more precisely formulated award criteria set out in **Annex VII** (Procedure for awarding specific contracts under the framework contract).

Signature of the framework contract imposes no obligation on the Agency to order services. Only the implementation of the framework contract through specific contracts is binding for the Agency.

Each specific contract will contain details of deliverables and timelines for particular services to be provided.

The Agency processes personal data in accordance with *Regulation (EU) 2018/1725 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC*. The tenderer is required to comply with the provisions of EU data protection legislation, in particular, *Regulation (EU) 679/2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation);* and shall provide sufficient guarantees to implement appropriate technical and organisational measures in such a manner that processing of personal data will also meet the requirements of Regulation (EU) 2018/1725 and ensure the protection of the rights of data subjects.

At reopening of competition stage, and depending on the specific research question and related deliverables, the Agency may request that the contractor provide a description and evidence of their data protection compliance system with a focus on summarising their technical and organisational

safeguards and security measures in place, as well as how compliance with relevant data protection provisions is ensured. Such description and evidence shall be an integral part of the resulting specific contract.

11.1. Implementation of the framework contract

1. Whenever the Agency decides that a research study in support of regulatory decision making is required, it will reopen the competition among all the framework contractors within a specific lot.
2. The Agency will draw up the technical specifications, including background information, details of deliverables and timelines.
3. The Agency will send these specifications by email to all framework contractors for the specific lot and specify a deadline (typically minimum 2 weeks) by which the technical and price offers need to be submitted to the Agency in the form of a detailed research proposal.
4. Within 5 working days of receipt of the specifications, the contractors shall send by email an acknowledgement of receipt and express their intention to carry out the services required. The contractors should provide justification in case they do not intend to submit an offer.
5. The contractors submit their technical and price offer, including proposal of subcontractor(s) within a minimum of two weeks, or other deadline which may be communicated by the Agency. Specific tenders are submitted by email to a secure mailbox where specific tenders are kept integer and confidential until the tender closing time and date or by any other mean specified in the request for service. The address of this mailbox will be communicated by the Agency with each invitation to tender. An automatic response will confirm receipt of the specific tender.
6. The Agency will assess the offers by a team of evaluators consisting of EMA staff and award the contract to the most economically advantageous tender, based on the award criteria provided in Annex VII of this document. The Agency also takes into account any conflicting interests which may negatively affect the performance of the specific contract.
7. The Agency will notify its decision to the contractor and may sign a specific contract with the contractor which has submitted the most advantageous offer. The specific contract shall confirm the charges payable for the research study performed.
8. Within 10 working days of a specific contract being sent by the Agency to the contractor, the Agency shall receive it back, duly signed and dated.

11.2. Research teams in the specific contract

A table with the composition of the team and the role of each member shall be provided by the contractor for each specific request.

As appropriate, and if requested by EMA, a declaration on professional conflicting interests shall be provided for each member of the proposed research team.

Any change of expert involved in the specific contract shall be notified to and agreed with the Agency, subject to assessment of professional conflicting interests in relation to the topic of the research request.

11.3. Deliverables of specific contracts

Typically, the contractor may be requested to provide the following deliverables, although this list may vary depending on the individual research question:

- **Preliminary study plan** (including feasibility assessment, if applicable)
- **Study protocol**
  (for Lots 4 and 5, the protocols should follow the format described in GVP Module VIII[4], section VIII.B.3.1.)
- **Study report**
  (for Lots 4 and 5, the reports should follow the format described in GVP Module VIII, section VIII.B.4.3.2.)
- **Manuscript** – the manuscript should be suitable for submission to a peer-reviewed medical journal and include the following standard disclaimer: "*This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties.*"

  The published article shall be available with open access.

The Agency expects that specific studies in Lot 3 (Statistical research), Lot 4 (Qualitative research) and Lot 5 (Pharmacoepidemiological research) are conducted in line with the ENCePP principles and tools for scientific independence and transparency, and as such are registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register[5]). The *ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies*[6] will be an integral part of the framework contract.

11.4. Results and intellectual property rights

The provisions on the use of the research results and ownership of the research results can be found in the draft framework contract (Article I.10 Exploitation of the results of the contract and Article II.13 Intellectual Property Rights). Tenderers are advised to familiarise themselves with these contractual provisions.

Notwithstanding any other term of the framework contract, or any resulting specific contract, the Contractor is granted a non-exclusive, irrevocable, royalty-free license to make use in future research and for teaching purposes of any study results generated for the Agency under the Contract. Furthermore, the Contractor shall have the freedom to publish without restriction any research results generated for the Agency under the Contract (see also Article I.15 Other special conditions of the draft framework contract).

The research results must be forwarded to EMA. The copyright of the study results will belong to the Agency; the Agency will in particular have the right to publish the results, including the structured final data.

At the time of submitting a tender to a re-opening of competition the tenderer must provide information about the scope of pre-existing materials, their source and when and how the rights to these materials have been or will be acquired. In the tender proposal all quotations or information

[4] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
[5] http://www.encepp.eu/encepp_studies/indexRegister.shtml
[6] http://www.encepp.eu/code_of_conduct/index.shtml

originating from other sources and to which third parties may claim rights have to be clearly marked (source publication including date and place, creator, number, full title etc.) in a way allowing easy identification.

The successful contractor, to which a specific contract is awarded following a re-opening of competition, will be requested to establish a list of all pre-existing rights and rights of creators and third parties on the results of this specific contract or parts thereof. This list must be provided no later than the date of delivery of the final deliverable that is subject of the specific contract. The Agency will provide a form for this purpose which must be attached to the final invoice.

12. Exclusion criteria

All tenderers and identified subcontractors shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, stating that they are not in one of the situations of exclusion listed in this Annex.

The successful tenderer (and each partner in the case of joint offers) shall provide the documents mentioned as supporting evidence in **Annex III** before signature of the contract and within a deadline given by the Agency. The Agency may request that supporting evidence be provided by subcontractors. In case of subcontracting, tenderers should note that there will be an obligation to replace a subcontractor if it is in an exclusion situation.

The Agency may waive the obligation of a tenderer to submit the documentary evidence referred to above if such evidence has already been submitted to it for the purposes of another procurement procedure of EMA and provided that the issuing date of the documents does not exceed one year and that they are still valid. In such a case the tenderer shall declare on its honour that the documentary evidence has already been provided in a previous procurement procedure and confirm that no changes in its situation have occurred.

IMPORTANT NOTICE: As the time limit for submitting the above-mentioned documentation is in general 10 calendar days from the notification of the contract award, we strongly recommend that the tenderer starts gathering the requested documents (especially in case of joint tender/subcontracting, including the relevant documents for consortium partners/subcontractors) as soon as possible in order to have the documents ready to be sent to the Agency in case it is awarded the contract. This will reduce the time line to sign the awarded contract with the Agency. However, the Agency shall not sign the contract with the successful tenderer until a standstill period of 10 calendar days has elapsed, running from the day after the simultaneous dispatch by email of the notification to tenderers (those rejected and the successful tenderer(s)).

13. Selection criteria: legal and regulatory capacity

13.1. Requirement

All tenderers must have authorisation to perform the contract under national law.

13.2. Evidence required

As part of their tender response, all tenderers (and each partner in the case of joint offers) and identified subcontractors shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, stating that they have the legal and regulatory capacity to pursue the professional activity needed for performing the contract to meet the requirement as stated in 13.1.

The tenderer (and each partner in case of joint offers) shall provide the following evidence listed below **upon request** by the Agency at any time during the procurement procedure:

- Authorisation to perform the contract under national law, as evidenced by inclusion in a relevant professional or trade register (except for international organisations), membership of a specific professional organisation, express authorisation of entry in the VAT register.

The Agency may request at any time during the procedure that supporting evidence be provided by subcontractors.

14. Selection criteria: financial and economic capacity

14.1. Requirement

- Tenderers must be financially feasible and in a stable financial position and have the economic and financial capacity to perform the contract.
- In order to be financially feasible, an entity must be able to demonstrate a favourable total score for the following: liquidity, capability to cover its short-term commitments; solvency, capability to cover its medium and long-term commitments; and profitability, generating profits, or at least with self-financing capacity.

14.2. Evidence required

As part of their tender response, all tenderers (and each partner in the case of joint offers) shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, stating that they fulfil the applicable financial and economic criteria set out in 14.1.

If the tenderer is a company and is otherwise required under the law of the State in which it is established to publish its accounts, it shall provide **upon request** by the Agency at any time during the procurement procedure, including from subcontractors if requested:

1. financial statements or their extracts for the last two financial years for which accounts have been closed;
2. a statement of overall turnover for the last two financial years available.

If, for some exceptional reason which the contracting authority considers justified, the tenderer is unable to provide the documentation mentioned, it may prove its financial and economic capacity by any other means which the contracting authority considers appropriate.

If the tenderer relies on the capacities of other entities (e.g. a parent company), a written undertaking on the part of those entities confirming that they will place the resources necessary for performance of the contract at the disposal of the tenderer for the period of the contract may be requested by the Agency. In such case the Agency may require that the successful tenderer(s) and such entities are jointly liable for the execution of the contract.

The Agency may waive the obligation of a tenderer to submit the documentary evidence referred to above if such evidence has been submitted to it for the purposes of another procurement procedure and provided that the documents are up-to-date.

The following ratios will be calculated to evaluate financial feasibility:

Ratio	Formula	Scoring 0	1	2
Liquidity	*Liquidity* Current assets – Stocks – Debtors > 1 year Short term debts	Below 50%	Between or equal 50% and 100%	Above or equal 100%
Solvency	*Financial independence* Own funds Total liabilities	Below 20%	Between or equal 20% and 40%	Above or equal 40%
	Debt ratio Own funds Medium- and long-term debts (MLT)	Below 30%	Between or equal 30% and 60%	Above or equal 60%
Profitability	*Coverage of deposits and borrowed funds by Self Financing Capacity (SFC*)* SFC Medium and long terms debt (MLT) * SFC = net result + amortisation	Below 25%	Between or equal 25% and 50%	Above or equal 50%
	Profitability Gross operating result Turnover	Below 5%	Between or equal 5% and 15%	Above or equal 15%

A score is awarded according to the calculated values of each of the five ratios and the maximum score an entity may obtain is a total of 10 points.

In order to meet the financial capacity criterion, the tenderer must obtain a score of at least 4 points out of 10.

If it seems that the financial feasibility evaluation does not provide a favourable picture of an organisation's financial status, economic and financial capacity may be proven by any other means which the contracting authority considers appropriate.

In case of joint tenders the financial and economic capacity shall be evaluated as a whole.

15. Selection criteria: technical and professional capacity

15.1. Requirements

The requirements are:

A. For each lot being tendered for, the tenderer must have experience in conducting research in the domain and have research commissioned by an external source.

B. The tenderer shall have access to a multi-disciplinary research team for each lot tendered. The team shall be led by (a) responsible senior investigator(s) with a strong (PhD level) academic background in one of the life sciences, and at least 5 years' experience in research.

C. Quality assurance processes within the company and suitable measures in place to ensure high quality service, especially with regard to access to or collection, validation of appropriate data relevant to the lot(s) tendered.

15.2. Evidence required

As part of their tender response, all tenderers (and each partner in the case of joint offers) shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, stating that they fulfil the applicable technical and professional criteria set out in section 15.1.

Any tenderer with a professional conflicting interest (see also Section 16.) which prevents it from performing the contract adequately may be rejected on the basis of not fulfilling selection criteria for professional capacity.

The tenderer shall provide the documents listed below **upon request** by the Agency at any time during the procurement procedure. For joint tenders the technical and professional capacity shall be evaluated in relation to the tender submitted as a whole, including all group members and subcontractors.

A. For each lot being tendered for, a list of links to relevant publications over the last three years in peer-reviewed journals, or study reports in the public domain, or documentation of relevant unpublished research comparable to the research described in this tender (see also: detailed lot and service descriptions in Section 3.3.). If more than one lot is being tendered for a combined list may be submitted but it must be grouped by lots.

B. A Curriculum Vitae showing the educational and professional qualifications, skills, experience and expertise of the responsible senior staff member who would lead the research team.

   If more than one lot is being tendered for, a separate CV is required per lot, unless the responsible senior staff member shall be the same for any lot, in which case this should be made clear.

   Curricula Vitae should be submitted without indication of any name. Each should bear a number only and the tender should include a separate list showing the association between these numbers and actual names.

C. Means available for ensuring quality: a list of data sets appropriate to the lot (see also: detailed lot and service descriptions in Section 3.3.) that the tenderer may have access to, including a description, per data set, of the type, setting, size, coverage and processes in place for data validation and data quality control. If more than one lot is being tendered for, a combined list may be submitted but it must be grouped by lots.

16. Professional conflicting interest

16.1. Requirements

The verification of professional conflicting interest under the selection criteria refers both to tenderers (including all partners in case of joint tenders) and subcontractors to be engaged in the provision of the service covered by the present procurement procedure. This verification will also apply to any additional subcontractor that is being proposed at the reopening of competition stage.

In accordance with Point 20.6 Annex 1 FR[7] the EMA may reject tenderers in case of professional conflicting interest that may negatively affect the performance of the framework or any resulting specific contract.

[7] Regulation (EU, Euratom) 2018/1046 on the financial rules applicable to the general budget of the Union

In its assessment EMA will take into consideration if the tenderer and/or subcontractor:

- is a marketing authorisation holder (MAH) or marketing authorisation applicant (MAA) within the territory of the EEA[8];
- is a manufacturer of a medicinal product for which there is a marketing authorisation or ongoing marketing authorisation application within the territory of the EAA.

A declared interest does not necessarily mean to constitute a professional conflicting interest. In its assessment EMA will apply the principle of proportionality laid down in Article 160 (1) Title VII, Chapter 1 FR.

16.2. Evidence required

The tenderer (including all partners in case of joint tenders) and the identified subcontractor(s) shall sign a declaration of honour stating that it/they is/are not in one of the situations of professional conflicting interest mentioned above (see **Annex III**).

A tender shall be rejected from the procurement procedure if the tenderer has misrepresented the information in this declaration of professional conflicting interests (Article 141(1)(b) FR). Rejection from the procedure on this ground may have serious consequences for the tenderer concerned as it may result in administrative and financial penalties based on grave professional misconduct (Article 136(1)(c) FR).

An assessment of professional conflicting interest based on the above criteria will be carried out by the EMA based on all the documents and information provided in the offer, in particular the evidence for the selection criteria. If necessary (e.g. in case of doubt), the EMA will ask for clarifications regarding the issue.

The tenderers shall note that if following the assessment, the tenderer is found to be in a situation of professional conflicting interest, the corresponding tender will not be further evaluated and will be rejected.

The tenderers and/or the subcontractor are obliged to report to the contracting authority any change in their situation related to the absence of professional conflicting interest throughout the implementation of the contract.

Tenderers shall note that they may be required to provide a detailed 'Declaration of professional conflicting interests' at each re-opening of competition with regard to the specific subject matter of the call.

17. Award criteria

In order to determine the most economically advantageous tender, the award criteria which will apply to this procurement procedure are as follows:

Qualitative award criteria:	70%
Price:	30%
Total	100%

[8] Legal or natural persons which control, i.e. own a majority stake in, (i) otherwise exercise a significant influence in the decision-making processes of the relevant MAH/MAA, (ii) are controlled by or (iii) are under common control of a MAH/MAA, shall be considered to be an MAH/MAA.

For joint tenders the award criteria shall be evaluated in relation to the tender submitted as a whole, including all consortium members and subcontractors.

17.1. Qualitative award criteria

Tenderers may apply for one or several of the six lots described in section 3.2.

The qualitative criteria which will apply equally to all six lots of this tender are set out in tabular format below, including the available points and minimum scores. Any tenderer not achieving the minimum scores indicated below will be eliminated and not evaluated for price. The qualitative award criteria shall account for **70% of the weighting** for this tender.

Generic responses and the mere repetition of mandatory requirements set out in these specifications, without going into details or without giving any added value, will result in a low score.

The sum of all quality award criteria gives a maximum possible of **70 points**.

No.	Qualitative award criterion	Weighting	Maximum points available	Minimum points, which must be achieved
A	Case study	35%	35	21
B	Research Team & Tasks	25%	25	15
C	Project management and communication	10%	10	6
	TOTAL	70%	70	42

A. Case study (35%)

This criterion will assess the tenderer's overall approach to addressing a request for a study to be conducted taking account of the regulatory context and the tenderer's knowledge of the most recent developments of appropriate methods. The proposal should introduce the scope, define the tasks and set out the preferred methodological approach - or outline a number of different possible approaches.

Tenderers are requested to submit a high-level proposal (max. four A4 pages each) for research in the hypothetical scenario(s) relating to each of their chosen lot(s) as described below. If considered helpful, any relevant supporting documents may be provided in an Annex.

Case study – Lot 1 (Pre-clinical research):

N-Nitrosamines are mutagenic substances classified as probable human carcinogens which have been identified as impurities in several medicinal products. Consider the situation where the marketing authorisation holder of a nitrosamines-containing medicinal product has been requested to identify the risk of carcinogenicity due to the presence of nitrosamine impurities.

Where valid carcinogenicity studies (usually 2-year rodent bioassays) are available, compound specific limits for nitrosamines can be extrapolated to a theoretical human risk using the TD50 calculated from the carcinogenicity study as a point of departure. Valid carcinogenicity data are not available however for many of the nitrosamines identified or potentially present in drug products. In addition, there are gaps in our understanding as to how the impurities arise in the manufacturing process.

Toxic effects emanating from N-nitrosamines may not only affect human patients, but also consumer health in case food-producing species (e.g. cattle and swine) are treated with potentially nitrosamine-containing veterinary medicinal products. In addition, companion animals may also be affected by the administration of contaminated veterinary medicinal products. In order to allow for the assessment of the potential risk to the consumer or target animals, different aspects have to be taken into account, for instance, metabolic capacity in relevant tissues as well as toxicokinetic and toxicodynamic parameters of various N-nitrosamines in food and non-food-producing target animals and/or the consumer (e.g. residues of N-nitrosamines or of genotoxic metabolites).

Please describe the approach you will follow for the design and implementation of possible studies that will allow improved risk evaluation of nitrosamine impurities in human and veterinary medicinal products. These should include literature studies as well as studies generating new in vitro or in vivo experimental data on:

- the ability of N-nitrosamine to be metabolically activated
- the metabolic competence and capacity of the tissue to form diazonium/carbenium ions
- the nature and stability of the diazonium/carbenium ion and the DNA-adducts formed
- the capacity, velocity and accuracy of the different cellular repair mechanisms responsible for the repair of the different DNA-adducts in tissues
- the proliferative activity of the tissues exposed
- the utility of in vitro and in vivo mutagenicity assays to predict human carcinogenicity
- expert systems to predicts the potential mutagenicity and carcinogenicity of nitrosamines through structure activity relationship analysis.

Case study – Lot 2 (Veterinary studies):

In the EU, wild bird populations have been in constant decline in the last two decades. Aside from occasional infectious disease outbreaks, it is believed that current agricultural practices as well as the intense use of pesticides are the main reasons for this phenomenon. Apart from the application of biocidal products, residues of chemical substances found in the environment may also originate from the administration of veterinary medicinal products to livestock and other domestic animals. However, up to now, the extent to which certain veterinary medicinal products (e.g. parasiticides) may contribute to the decline of wild avian populations is not fully elucidated yet. While toxicological effects emanating from well-established (active) substances contained in certain veterinary medicines have been quite abundantly studied, data on their overall environmental distribution and occurrence in certain environmental compartments as well as effects on non-target populations (e.g. wild birds, insects and bacteria) are less common. In addition, the assessment of the potential toxic effects of certain veterinary medicinal products on wild bird populations through environmental exposure is hampered by the fact that some active substances used in those products are also used as active principles in biocidal products. Finally, it is not clear to what extent the occurrence of residues of certain veterinary medicinal products in wild birds from which foodstuffs have been derived (e.g. though hunting) might pose a safety/health concern for the consumer ingesting such food products.

The applicant is invited to suggest studies that would allow the assessment of the impact that the use of certain veterinary medicinal products in livestock or domestic animals may have on wild avian populations across the EU. The proposed retrospective or prospective study should mainly be based on available databases or on data available from published literature. Alternatively, existing databases could be supplemented with new epidemiological studies in which data are generated to address the research question(s) outlined below.

One or more of the following aspects should be addressed:

- The relevance of certain classes of veterinary medicinal products in regard to the observed decline of wild avian populations.
- The toxicity of new (i.e. not well established) active substances contained in relevant veterinary medicinal products towards wild avian species.
- The occurrence of residues of active substances contained in relevant veterinary medicinal products in different environmental compartments relevant to the habitat of wild avian species, including potential adverse effects on non-target populations as well as towards the consumer potentially ingesting food products derived from wild birds.
- The occurrence and persistence of residues of active antimicrobial or antiparasitic substances contained in relevant veterinary medicinal products in the environment and their effect on the development of antimicrobial-resistant bacteria and resistance genes or antiparasitic-resistant parasites and related resistance genes in the environment as well as their consequences for animal and public health.
- The occurrence of residues of active substances contained in relevant veterinary medicinal products in wild avian species and their offspring, including potential adverse effects.
- The potential sensitivity/susceptibility of certain wild avian species towards certain active substances contained in relevant veterinary medicinal products, including potential adverse effects.
- Approaches allowing the differentiation of whether a residue measured in a certain animal or environmental compartment originates from the use of a relevant veterinary medicinal products or medicinal products for human use or other products used, for instance, in animal husbandry.
- The pattern of use of relevant veterinary medicinal products in livestock or other domestic animals, including doses regimes, duration of treatment and total amounts, animal species treated as well as potential adverse effects emanating from such usage patterns.
- The monitoring and reporting of adverse effects derived from the use of veterinary medicinal products in target and non-target populations (e.g. wild birds) or in the environment via relevant pharmacovigilance databases/systems.

Please describe the approach you will follow for the design and implementation of the study that will address one or more of the areas outlined above (including definition of exposure, outcomes and other variables), as well as the methods proposed for the analysis, interpretation and reporting of the results. A list of databases that can be accessed by the tenderer should be provided. The lag time of the proposed databases for the possible evaluation of a safety signal for this new drug should be provided and briefly discussed.

Case study – Lot 3 (Statistical research):

Randomised controlled trials remain the most important trial design in the evaluation of marketing authorisation applications. At the same time, the changing nature of drugs as well as advances in technology and data collection systems have increased the interest in innovative clinical trial designs which are thought to respond to specific patient needs where traditional trial designs are not feasible or more difficult to perform.

Please consider the situation where the EMA, in order to advise pharmaceutical companies on the use of innovative trial designs, launches a project to analyse the merits and potential challenges of innovative approaches for drug development. Innovative approaches for drug development of interest

include, but are not limited to, platform trials, in silico trials, decentralised trials or trials that involve the use of real-world data.

Please select at least two innovative clinical trial designs, explaining for each design:

- the methodological challenges to be addressed;
- what type of statistical research you would perform to address each of the methodological challenges;
- the approach you would follow for this research, e.g. through simulation, modelling or using data from clinical trials or other data sources;
- under which circumstances the trial design might be used to generate evidence in the context of regulatory decisions on the benefit-risk profile of new medicinal products.

Case study – Lot 4 (Qualitative research):

Following an in-depth evaluation, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that a medicinal product authorised for depression may be associated with congenital malformations and neurodevelopmental disorders when used during pregnancy (hypothetical scenario). Risk minimisation measures included restrictions of the use of the product in women as a second line treatment for severe depression and the introduction of a pregnancy prevention programme (PPP) requiring effective contraception in women for whom the product is the only option after trying other treatments, a pregnancy test at each prescription of the product, the provision of educational materials (including a patient information booklet, a checklist for prescribers, a checklist for patients and an information acknowledgement form) to all health care professionals (HCPs) and female patients, and a regularly review of the need of the prescription of the product.

The PRAC also recommended to perform a study assessing:

- the dissemination process and receipt of all the information described above by patients and HCPs
- risk awareness, knowledge and relevant attitudes of patients
- risk awareness, knowledge and relevant attitudes of HCPs
- change of behaviours in healthcare in accordance with the PPP, which should also address behaviours such selection of antidepressive therapy in women of childbearing potential, performing regular medication reviews, patient counselling using risk minimisation materials, performance of pregnancy testing and the use of effective contraception
- unintended effects such as suboptimal management of depression in women, whether of child-bearing potential or not.

The study should be performed in at least three Member States.

Please describe the approach you will follow for the design and implementation of the study, the data sources and methods proposed for the analysis, interpretation and reporting of the results, how you will reach out to patient and HCP communities and any specific tools/techniques to be used in the study. Explain if and how you intend to consult patients and HCPs on the design of the study in terms of appropriateness and feasibility, how you will ensure data saturation and robustness of insights gained, and how you will ensure the regulatory relevance of the evaluation of the PPP in terms of investigating and suggesting areas of improvement action within the regulatory mandate.

Case study – Lot 5 (Pharmacoepidemiological research):

In the example below, Newstatin is not a real drug.

A safety signal of peripheral neuropathy has been identified from spontaneous reports in EudraVigilance with the drug Newstatin, a novel substance belonging to the class of HMG-CoA reductase inhibitors. Although peripheral neuropathy is a rare adverse reaction already known with statins, the EMA is concerned that peripheral neuropathy may occur more frequently than for other statins and may lead to early cessation of treatment, with a possible increased risk of cardiovascular diseases. In the context of the signal evaluation and to inform regulatory decisions as regards possible risk minimisation activities, the EMA considers that additional evidence is needed on the use of Newstatin in Europe and the potential risk of peripheral neuropathy. A study is launched to collect the following information in at least three EU Member States:

- Incidence and prevalence of exposure to Newstatin stratified by age, gender, duration of exposure and cumulative dose
- Incidence of peripheral neuropathy in incident patients exposed to Newstatin, stratified by age, gender, duration of exposure, cumulative dose and high-risk populations
- Estimation of the relative risk of peripheral neuropathy in patients exposed to Newstatin in comparison to comparator patients, taking into account duration of exposure, dose and other risk factors for peripheral neuropathy
- Estimation of the proportion of patients who discontinue Newstatin due to the occurrence of peripheral neuropathy and i) are switched to other anti-lipid medication, ii) remain free of anti-lipid medication.

Please explain the study design and the statistical analysis that you would use to address each objective of this study, including the definition of exposure, outcomes and other variables. A list of databases that can be accessed by the tenderer should be provided. The lag time of the proposed databases for the possible evaluation of a safety signal for this new drug should be provided and briefly discussed.

Case study - Lot 6 (Quality of medicines):

There are significant uncertainties with regard to the origin of a highly potent mutagenic impurity detected in medicines containing the substance "madeupname" (MUN) (hypothetical scenario). Possible sources are an impurity generated during manufacture, a degradant of the active pharmaceutical ingredient when exposed to an undetermined reagent, an auto-degradation product, an in vivo metabolite, an analytical artefact or a combination of one or more of the above. In order to deconvolute these root causes, a series of physical organic chemistry experiments could be conducted. These could include kinetic, isotopic labelling and pharmacokinetic studies, for example:

- differential isotopic labelling of both termini of the MUN molecule using well-designed synthetic processes
- competition experiments of isotopically labelled MUN including with exogenous unlabelled nitrite
- PK studies of labelled MUN
- Kinetic measurements of MUN rates of formation
- Spectroscopic and spectrometric analysis of reaction mechanism(s)

Please describe the approach you would follow for the design and conduct of the studies, the different experiments and the methods proposed for the analysis, interpretation and reporting of the results.

B. Research team & tasks (25%)

Tenderers are requested to submit a description of the proposed research team roles and distribution of tasks, including the rationale behind the choice of this allocation (max. two A4 pages per lot, preferably in tabular form). This description should relate to a typical research assignment, and not to a particular study.

This criterion will assess how the roles and responsibilities of the proposed team (including subcontractors, if applicable) are distributed for each task, e.g. in protocol development, data extraction and data analysis, interpretation of results, writing of study report and manuscript, etc.

It also assesses the global allocation of resources to the project and to each task or deliverable, and whether this allocation is adequate for the work.

Individuals should not be identified by name, and no Curricula Vitae should be submitted in response to this criterion.

C. Project management & communication (10%)

Tenderers are requested to submit a high-level description of the related project management processes and proposed communication activities, including policy on conflicts of interest (max. two A4 pages per lot). Tenderers are requested to include a description of the mechanisms for assuring a continuous service and quality of deliverables, rapid response and timely availability of the specific expertise required for covering services to be implemented under the Framework Contract. The tenderer's policy on conflicts of interest should also be described. This description should relate to a typical research assignment, and not to a particular study.

This criterion will assess the general processes in place to manage research projects including the quality control system applied to the service foreseen with regard to

- quality of deliverables,
- mechanisms to ensure the committed level of expertise and resources throughout the whole duration of the contract,
- management of agreed timelines,
- strategies to overcome difficulties in meeting deadlines and contingency planning (e.g.in case of absence of a team member),
- policy on conflicts of interest.

17.2. Price

Only those tenderers which have obtained the stipulated minimum score shall be evaluated for price and thus for award of the contract.

Price shall account for **30%** of the weighting for this procurement procedure.

The award criteria for price shall be evaluated according to the following formula:

$$\frac{\text{Lowest price x weighting for price}}{\text{Tenderer's price}}$$

For the purposes of evaluation, ”price” in this formula shall be the grand total for the hypothetical specific service assignment per lot in the appropriate costing sheets in **Annex II.1 to II.6** calculated to two decimal places.

Tenderers’ attention is drawn to Article 23 of Annex I to Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, concerning abnormally low tenders.

17.3. Total points for award criteria

Following evaluation of price, the points for the qualitative award criteria and the points for price shall be added together to arrive at a grand total to two decimal places. Per each lot tenders shall be ranked according to the best price-quality ratio in accordance with the formula below:

Score for tender X = (cheapest price / price of tender X)*30 + (total quality score tender X / 70)*70

A contract shall be awarded to the first 10 (ten) ranked tenders per lot which comply with the minimum requirements specified in the procurement documents and are submitted by tenderers with access to procurement, not in an exclusion situation and fulfilling the selection criteria. The ranking will determine who will be invited to compete for specific contracts during the implementation of the framework contract.

18. Tender to be submitted

Tenders are to be submitted via the eSubmission application according to the detailed instructions laid down in section 1. Submission of tenders of the invitation to tender letter and the eSubmission Quick Guide[9]. Tenderers are reminded to prepare and submit their electronic tender in eSubmission early enough to ensure it is received within the deadline specified under Heading IV.2.2 of the contract notice.

Tenderers willing to submit tenders for more than one lot need to upload a separate technical and financial offer for each of the lots in which they are interested.

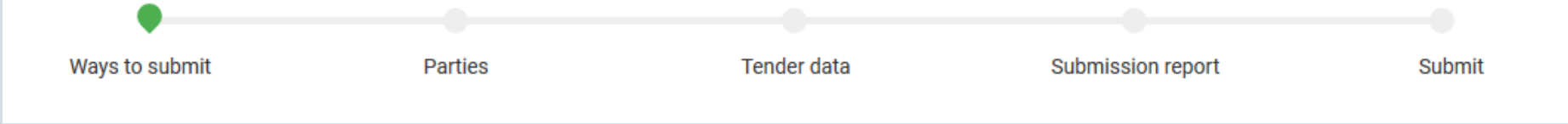
In eSubmission the identification of the participant and definition of the parties is a step that occurs before the selection of the lots. Therefore, if the composition of the consortium is different per lot, separate submissions per lot are required.

Where a document needs to be signed, the signature must be either hand-written or a qualified electronic signature as defined in Regulation (EU) No 910/2014 on electronic identification and trust services for electronic transactions in the internal market (the eIDAS Regulation)[10].

A list of documents that tenderers must submit with the tender or during the procedure can be found in the Appendix.

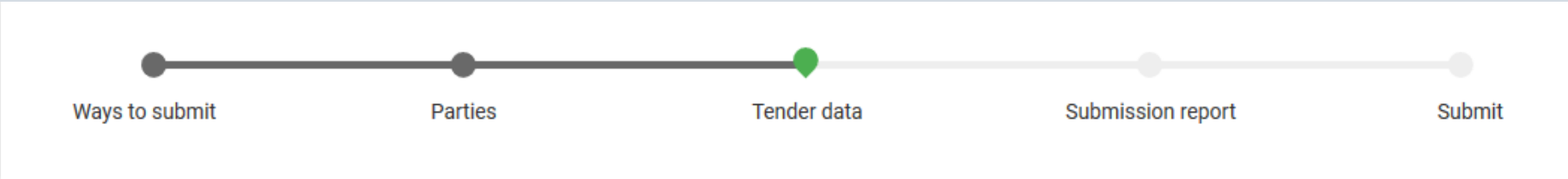
[9] https://ec.europa.eu/info/funding-tenders/opportunities/docs/esubmission/quickguidepp_en.pdf
[10] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2014.257.01.0073.01.ENG

Appendix: List of documents to be submitted with the tender or during the procedure

Description	Sole tenderer	Joint tender		Identified Subcontractor	When and where to submit the document?	Instructions for uploading in eSubmission (if applicable)	
		Group leader	Member of the group			How to name the file?	Where to upload?
1. Identification and information about the tenderer ***eSubmission view*** 							
Cover letter joint tender OR sole tender (see Annex Ia and Ib)	☒	☒			With the tender in eSubmission	'Cover letter'	In the Group leader's or Sole tenderer's section under 'Parties' →'Identification tenderer' →'Attachments' →'Other documents'
Overview indicating clearly the identity, roles, activities and responsibilities of each individual partner		☒			With the tender in eSubmission	'Group overview'	In the Group leader's section under 'Parties' →'Identification tenderer' →'Attachments' →'Other documents'
Declaration on Honour on Exclusion and Selection Criteria, including professional conflicting interest (see Annex III)	☒	☒	☒	☒	With the tender in eSubmission	'Declaration on Honour'	With the concerned entity under 'Parties' →'Identification tenderer' →'Attachments' →'Declaration on Honour'

Description	Sole tenderer	Joint tender		Identified Subcontractor	When and where to submit the document?	Instructions for uploading in eSubmission (if applicable)	
		Group leader	Member of the group			How to name the file?	Where to upload?
Minimum technical requirements declaration (see Section 3.5 and Annex IV) + Lot 5 data access documentation (if applicable)	☒	☒			With the tender in eSubmission	'Minimum requirements declaration' 'Lot 5 data access'	In the Group leader's or Sole tenderer's section under 'Parties' →'Identification tenderer' →'Attachments' →'Other documents'
List of identified subcontractors (see Annex V)	☒	☒			With the tender in eSubmission	'List of identified subcontractors'	In the Sole tenderer's or the Group leader's section under 'Parties' →'Identification tenderer' →'Attachments' →'Other documents'
Letter of intent signed by each identified subcontractor				☒	With the tender in eSubmission	'Letter of intent'	With the concerned entity under 'Parties' →'Identification tenderer' →'Attachments' →'Other documents'
Evidence of non-exclusion (see Section 12) Applies to all tenderers (and each partner in the case of joint offers). [The Agency may request that supporting evidence be provided by subcontractors at any time during the procedure.]	☒	☒	☒	[☒]	Only upon request by EMA At any time during the procedure	n.a.	n.a.

Description	Sole tenderer	Joint tender		Identified Subcontractor	When and where to submit the document?	Instructions for uploading in eSubmission (if applicable)	
		Group leader	Member of the group			How to name the file?	Where to upload?
Evidence of legal capacity (see Section 13) Applies to all tenderers (and each partner in the case of joint offers). [The Agency may request that supporting evidence be provided by subcontractors at any time during the procedure.]	☒	☒	☒	[☒]	Only upon request by EMA At any time during the procedure	n.a.	n.a.
Evidence of economic and financial capacity (see Section 14)	**The documents must be provided only by the involved entities who contribute to reaching the financial and economic capacity.**				Only upon request by EMA At any time during the procedure	n.a.	n.a.
Evidence of technical and professional capacity (see Section 15)	**The documents must be provided in relation to the tender submitted as a whole, including all group members and subcontractors.**				Only upon request by EMA At any time during the procedure	n.a.	n.a.

Description	Sole tenderer	Joint tender		Identified Subcontractor	When and where to submit the document?	Instructions for uploading in eSubmission (if applicable)	
		Group leader	Member of the group			How to name the file?	Where to upload?
2. Tender data. ***eSubmission view***  ***Failure to upload the following documents in eSubmission will lead to rejection of the tender.***							
Technical offer (see Section 17)	☒	☒			With the tender in eSubmission	'A Case study_Lot [number]' 'B Team' 'C Management'	Under section 'Tender Data' →'Technical offer'
Financial offer (see Section 9 and Annex II.1 - 6)	☒	☒			With the tender in eSubmission	'Financial offer_Lot [number]'	Under section 'Tender Data' →'Financial offer'