EUROPEAN
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ANNEXES 1 to 3

ANNEXES

to the

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health and amending Regulations (EC) No 178/2002, (EC) No 1394/2007, (EU) No 536/2014, (EU) 2019/6, (EU) 2024/795 and (EU) 2024/1938 (European Biotech Act)

{SWD(2025) 1055 final}

ANNEX I

Biotechnology Products of Concern

1. Benchtop nucleic acid synthesis equipment

Any instrument designed, marketed or configured to *de novo* synthesise nucleic acids (DNA, RNA) or their base-pairing analogues, including LNA, PNA and XNA, by chemical or enzymatic means for use by an individual user, laboratory or facility.

2. Sequences of concern

Molecules of polymeric nucleic acids that have been synthesized *de novo* (without template), including single- or double-stranded RNA or DNA that is at least 50 nucleotides in length, or the corresponding amino acid sequence of at least 17 amino acids, and meets at least one of the following criteria:

(a) is an exact match or best match to a sequence of an agent listed on internationally recognised control lists that is either (i) specific to any listed virus or (ii) specific to any listed bacterium that, in itself or through its transcribed or translated products represents a significant hazard to human, animal or plant health. This criterion shall exclude cases where the matched sequence is a non-harmful element demonstrably present in an unregulated agent, including housekeeping genes without pathogenic function;

(b) is reasonably expected, based on international standards, current scientific evidence and industry best practices for predicting biological function from sequence, to increase a biological agent's ability to be used to deliberately cause disease or death, by contributions to pathogenicity, toxicity, or other criteria, even if not derived from a listed agent;

(c) has the potential to be assembled into a sequence that is at least 200 nucleotides in length and meets point (a) or (b) if combined with other synthetic nucleic acids supplied by the same economic operator to that customer in a bulk order or across multiple orders over the previous12 months.

ANNEX II

Annexes to Regulation (EU) 536/2014 are amended as follows:

(1) Annex I is replaced by the following:

‘Annex I

Part I

A. INTRODUCTION AND GENERAL PRINCIPLES

1. The sponsor shall, where appropriate, refer to any previous applications. If these applications have been submitted by another sponsor, the written agreement from that sponsor shall be submitted.

2. Where a clinical trial has more than one sponsor, detailed information of the responsibilities of each of the sponsors shall be submitted in the application dossier.

3. The application shall be signed by the sponsor or a representative of the sponsor. This signature confirms that the sponsor is satisfied that:

   (a) the information provided is complete;

   (b) the attached documents contain an accurate account of the information available;

   (c) the clinical trial is to be conducted in accordance with the protocol; and

   (d) the clinical trial is to be conducted in accordance with this Regulation.

4. The application dossier for an application limited to Part I of the assessment report referred to in Article 11 shall be limited to sections B to J and Q of this Annex.

5. (deleted)

B. COVER LETTER

6. The cover letter shall specify the EU trial number and the universal trial number and shall draw attention to any features which are particular to the clinical trial.

7. However, in the cover letter it is not necessary to reproduce information already contained in the EU application form, with the following exceptions:

   (a) specific features of the clinical trial population, such as subjects not able to give informed consent, minors and pregnant or breastfeeding women;

   (b) whether the clinical trial involves the first administration of a new active substance to humans;

   (c) whether scientific advice relating to the clinical trial or the investigational medicinal product has been given by the Agency, a Member State or a third country;

   (d) whether the clinical trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006 (if the Agency has already issued a decision on the PIP, the cover letter contains the link to the decision of the Agency on its website);

(e) whether investigational medicinal products or auxiliary medicinal products are a narcotic, psychotropic or radiopharmaceutical;

(f) whether the investigational medicinal products consist of or contain a genetically-modified organism or organisms;

(fbis) whether the investigational medicinal products consist or contain genetically-modified organism(s) and, where applicable, whether they fall within one or more of the categories listed in Article 4a(1), points (a) to (d), of Regulation(EC) No 1394/2007;

(g) whether the sponsor has obtained an orphan designation for the investigational medicinal product for an orphan condition;

(h) a comprehensive list, including the regulatory status, of all investigational medicinal products and a list of all auxiliary medicinal products; and

(i) a list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use.

8. The cover letter shall indicate where the information listed in paragraph 7 is contained in the application dossier.

9. The cover letter shall indicate if the clinical trial is considered by the sponsor to be a minimal or low-intervention clinical trial and shall contain a detailed justification thereof.

10. The cover letter shall indicate if the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial, and as a consequence whether informed consent will be obtained by simplified means.

11. The cover letter shall indicate the location in the application dossier of the information necessary for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction, that is the reference safety information.

12. In the case of a resubmission, the cover letter shall specify the EU trial number for the previous clinical trial application, highlight the changes as compared to the previous submission and, if applicable, specify how any unresolved issues in the first submission have been addressed.

12a. The cover letter shall include a summary of the activities that are planned to conduct outside traditional trial sites, enabled by digital technologies, remote procedures, and alternative delivery models in clinical trials.

C. EU APPLICATION FORM

13. The EU application form duly completed.

D. PROTOCOL

14. The protocol shall describe the objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial.

15. The protocol shall be identified by:

(a) the title of the clinical trial;

(b) the EU trial number;

(c) the sponsor's protocol code number specific for all versions of it (if relevant);

(d) the date and number of the version, to be updated when it is amended;

(e) a short title or name assigned to the protocol; and

(f) the name and address of the sponsor, as well as the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol.

16. The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.

17. The protocol shall at least include:

(a) a statement that the clinical trial is to be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice;

(b) a comprehensive list of all investigational medicinal products and of all auxiliary medicinal products;

(c) a summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial;

(d) a summary of the known and potential risks and benefits including an evaluation of the anticipated benefits and risks to allow assessment in accordance with Article 6; for subjects in a clinical trial in an emergency situation, the scientific grounds for expecting that the participation of the subjects has the potential to produce a direct clinically relevant benefit shall be documented;

(e) where patients were involved in the design of the clinical trial, a description of their involvement;

(f) a description of, and justification for, the dosage, the dosage regime, the route and mode of administration, and the treatment period for all investigational medicinal products and auxiliary medicinal products;

(g) a statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;

(h) a description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example. age, gender, participation of healthy volunteers, subjects with rare and ultra rare diseases;

(i) references to literature and data that are relevant to the clinical trial, and that provide background for the clinical trial;

(j) a discussion of the relevance of the clinical trial in order to allow assessment in accordance with Article 6;

(k) a description of the type of clinical trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);

(l) a specification of the primary end-points and the secondary endpoints, if any, to be measured during the clinical trial;

(m) a description of the measures taken to minimise bias, including, if applicable, randomisation and blinding;

(n) a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant;

(o) a clear and unambiguous definition of the end of the clinical trial in question and, if it is not the date of the last visit of the last subject, a specification of the estimated end date and a justification thereof;

(p) a description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial;

(q) arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant;

(r) a description of procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data;

(s) a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document;

(t) a description of the arrangements for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product in accordance with Article 51;

(u) a description of the statistical methods to be employed, including, if relevant:

- timing of any planned interim analysis and the number of subjects planned to be enrolled;
- reasons for choice of sample size;
- calculations of the power of the clinical trial and clinical relevance;
- the level of significance to be used;
- criteria for the termination of the clinical trial;
- procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan; and
- the selection of subjects to be included in the analyses;

(v) a description of the subject inclusion and exclusion criteria, including criteria for withdrawing individual subjects from treatment or from the clinical trial;

(w) a description of procedures relating to the withdrawal of subjects from treatment or from the clinical trial including procedures for the collection

of data regarding withdrawn subjects, procedures for replacement of subjects and the follow-up of subjects that have withdrawn from treatment or from the clinical trial;

(x) a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;

(y) a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria;

(z) a detailed description of the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent;

(aa) a description of the treatments, including medicinal products, which are permitted or not permitted, before or during the clinical trial;

(ab) a description of the accountability procedures for the supply and administration of medicinal products to subjects including the maintenance of blinding, if applicable;

(ac) a description of procedures for monitoring subject compliance, if applicable;

(ad) a description of arrangements for monitoring the conduct of the clinical trial;

(ae) a description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question;

(af) a specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing these parameters;

(ag) a description of ethical considerations relating to the clinical trial if those have not been described elsewhere;

(ah) a statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial are to permit clinical trial- related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents;

(ai) a description of the publication policy;

(aj) duly substantiated reasons for the submission of the summary of the results of the clinical trials after more than one year;

(ak) a description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

(al) a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects;

(am) a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

(an) justification of allowing for a direct delivery to subject of an investigational medicinal products;

(ao) a detailed description of the management of investigational or auxiliary medicinal products delivered directly to the subject (‘direct delivery to subject’) shall be provided, including aspects of privacy protection and confidentiality. Information shall be included on ensuring that the product reaches the intended recipient (e.g., the participant or their designee) and on maintaining the integrity and quality of the medicinal product (e.g., blinding, storage) throughout the supply chain

(ap) a justification for inclusion of subjects that can only provide an informed consent through electronic means shall be provided.

(aq) if the sponsor used an AI tool, a clear explanation of the specific purpose of the use of that tool and a description of the processes in which it is used. If an AI tool is certified according to Regulation (EU) 2024/1689 laying down harmonised rules on artificial intelligence, the sponsor shall provide the information contained in the certificate.

18. If a clinical trial is conducted with an active substance available in the Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.

19. With regard to the notification of adverse events, the protocol shall identify the categories of:

(a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and

(b) serious adverse events which do not require immediate reporting by the investigator to the sponsor.

20. The protocol shall describe the procedures for:

(a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;

(b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;

(c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and

(d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

21. In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2), the protocol shall indicate the reasons thereof.

22. Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.

23. The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable.

24. The protocol shall be accompanied by a synopsis of the protocol.

E. INVESTIGATOR'S BROCHURE (IB)

25. An IB, which has been prepared in accordance with the state of scientific knowledge and international guidance, shall be submitted.

26. The purpose of the IB is to provide the investigators and others involved in the clinical trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

27. The information in the IB shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. It shall be prepared from all available information and evidence that

    supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the clinical trial and be presented in the form of summaries.

28. If the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the IB. If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the investigational medicinal product in the clinical trial. Where the investigational medicinal product is identified in the protocol only by its active substance, the sponsor shall select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

29. For a multinational clinical trial where the medicinal product to be used in each Member State concerned is authorised at national level, and the SmPC varies among Member States concerned, the sponsor shall choose one SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.

30. If the IB is not an SmPC, it shall contain a clearly identifiable section called the ‘Reference Safety Information’ (RSI). In accordance with paragraphs 10 and 11 of Annex III, the RSI shall contain product information on the investigational medicinal product and on how to determine what adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions.

F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT

31. As regards documentation relating to GMP compliance, the following shall apply.

32. No documentation needs to be submitted where the investigational medicinal product is authorised and is not modified, whether or not it is manufactured in the Union.

33. If the investigational medicinal product is not authorised, and does not have a marketing authorisation from a third country that is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is not manufactured in the Union, the following documentation shall be submitted:

    (a) a copy of the authorisation referred to in Article 61; and

    (b) certification by the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union, unless there are specific arrangements provided for in mutual recognition agreements between the Union and third countries.

34. In all other cases, a copy of the authorisation referred to in Article 61 shall be submitted.

35. For processes related to investigational medicinal products set out in Article 61(5), which are not subject to an authorisation in accordance with Article 61, documentation to demonstrate compliance with the requirements referred to in Article 61(6) shall be submitted.

G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

36. The IMPD shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.

36bis. Where applicable, in the case of advanced therapy investigational medicinal products, a declaration of the sponsor, in accordance with Article 4a(2) of Regulation (EC) No 1394/2007.

36.1. Data relating to the investigational medicinal product

Introduction

37. Regarding data, the IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details of this ‘simplified IMPD’ are set out in section 1.2 ‘Simplified IMPD by referring to other documentation’.

38. Each section of the IMPD shall be prefaced with a detailed table of contents and a glossary of terms.

39. The information in the IMPD shall be concise. The IMPD must not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

Quality data

40. Quality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format.

Non-clinical pharmacology and toxicology data

41. The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any investigational medicinal product used in the clinical trial in accordance with international guidance. It shall contain a reference list of studies conducted and appropriate literature references. Wherever appropriate, it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points. The summaries of the studies conducted shall allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

42. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format.

43. The IMPD shall provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

44. The IMPD shall contain a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3).

45. The test material used in toxicity studies shall be representative of that of the clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material shall be subject to the controls necessary to ensure this and thus support the validity of the study.

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Data from previous clinical trials and human experience

46. Data from previous clinical trials and human experience shall be submitted in a logical structure, such as that of Module 5 of the ICH Common Technical Document format.

47. This section shall provide summaries of all available data from previous clinical trials and human experience with the investigational medicinal products.

    It shall also contain a statement of the compliance with good clinical practice of those previous clinical trials, as well as a reference to the public entry referred to in Article 25(6).

Overall risk and benefit assessment

48. This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the investigational medicinal product in the proposed clinical trial unless this information is already provided in the protocol. In the latter case, it shall cross-refer to the relevant section in the protocol. The text shall identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults shall take account of the specific provisions set out in this Regulation.

49. Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the investigational medicinal product, preferably based on 'area under the curve' (AUC) data, or peak concentration (C_{max}) data, whichever is considered more relevant, rather than in terms of applied dose. The clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials shall also be discussed.

49.1. Simplified IMPD by referring to other documentation

50. The applicant may refer to other documentation submitted alone or with a simplified IMPD.

Possibility of referring to the IB

51. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the reference safety information and the summaries of pre- clinical and clinical parts of the IMPD. In the latter case, the summaries of pre-clinical information and clinical information shall include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the investigational medicinal product and the safety of its use in the proposed clinical trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the pre-clinical and clinical information shall be submitted as part of the IMPD.

Possibility of referring to the SmPC

52. The applicant may submit the version of the SmPC valid at the time of application, as the IMPD if the investigational medicinal product is authorised. The exact requirements are detailed in Table 1. Where new data are provided, it should be clearly identified.

▼B

Table 1: Content of the simplified IMPD

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The investigational medicinal product is authorised or has a marketing authorisation in an ICH country and is used in the clinical trial:			
	SmPC		
— within the conditions of the SmPC	SmPC	If appropriate	If appropriate
	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the investigational medicinal product is authorised or has a marketing authorisation in an ICH country and the investigational medicinal	SmPC+P+A	Yes	Yes
The investigational medicinal product is not authorised and has no marketing authorisation in an ICH country but the active substance is contained in an authorised medicinal product, and			
	SmPC+P+A	Yes	Yes
— is supplied by the same	SmPC+S+P+A	Yes	Yes
The investigational medicinal product was subject to a previous clinical trial application and authorised in at least 2 Member States and has not been modified, and			
	Reference to previous submission		
— no new data are available since last amendment to the clinical trial application,	New data	New data	New data
— new data are available since	If appropriate	If appropriate	If appropriate

(S: Data relating to the active substance; P: Data relating to the investigational medicinal product; A: Additional information on Facilities and Equipment, Adventitious Agents Safety Evaluation, Novel Excipients, and Solvents for Reconstitution and Diluents)

53. If the investigational medicinal product is defined in the protocol in terms of active substance or ATC code (see above, paragraph 18), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance pertaining to that ATC group. Alternatively, the applicant may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an investigational medicinal product in the clinical trial.

1.3. IMPD in cases of placebo

54. If the investigational medicinal product is a placebo, the information requirements shall be limited to quality data. No additional documentation is required if the placebo has the same composition as the tested investigational medicinal product (with the exception of the active substance), is manufactured by the same manufacturer, and is not sterile.

Ga – CORE DOSSIER

54a**.** The IMP-CD as a tool to support the development of the investigational medicinal product shall gather information relevant to regulatory processes. The IMP-CD shall describe the scope of authorised use in clinical trials, including the intended population(s), route(s) and mode(s) of administration, dosage range(s), exposure range, development stage(s), and as appropriate, relevant parameters that determine its applicability to clinical trials.

The IMP-CD contains product specific data and information in the IB and IMPD in agreement with Annex I points E and G. GMP-related documentation may be included in accordance with Annex I point F.

When using a reference to an approved IMP-CD in a clinical trial application, the sponsor shall confirm that the intended corresponding clinical trial falls within its defined scope as described in point 1.

Complementary, clinical trial specific information may be provided in the application dossier of the corresponding clinical trial.

Gb – POSSIBILITY TO REFERR TO SIMPLIFIED IMPD

54b. Possibility to refer to an active substance master file, an additional master file, a platform technology master file or a corresponding certificate, or a certificate confirming that the quality of the substance is suitably controlled by the relevant monograph of the European Pharmacopeia, or a certified platform technology master file as referred to in [REVISED Directive 2001/83/EC]. Where applicable, the sponsor may, instead of submitting all the relevant information on the quality of the active substance or any other substance present or used in the manufacture of the investigational medicinal product, include in the IMPD quality section an active substance master file (ASMF), or any other additional quality master file or a corresponding valid certificate, or a certificate confirming that the quality of the substance is suitably controlled by the relevant monograph of the European Pharmacopeia, or where relevant a certified platform technology master file as referred to in [revised Directive 2001/83/EC] provided that the active substance is produced in accordance with the master file or its certificate. Such reference shall be accompanied by a letter of access from the substance manufacturer when the substance is not manufactured by the sponsor. The manufacturer or certificate holder shall, however, provide the sponsor with all of the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the sponsor that it shall ensure batch to batch consistency. The holders of the master files or related certificates shall not modify the details of the master file without informing the sponsor. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities and sponsor, as

applicable. The sponsor shall include in the simplified IMPD any relevant data to the active substance or its manufacturing which is not covered in the referenced master file or certificate. In addition, all quality data relating to the investigational medicinal product and its manufacturing together with the non-clinical and clinical data shall be provided.

H. AUXILIARY MEDICINAL PRODUCT DOSSIER

55. Without prejudice to Article 65, the documentation requirements set out in sections F and G shall also apply to auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information is required.

I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

56. If available, a copy of the summary of scientific advice of the Agency, or of any Member State or third country, with regard to the clinical trial shall be submitted.

57. If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient (see section B).

J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

58. A description of the content of the labelling of the investigational medicinal product in accordance with Annex VI shall be provided.

Part II

General principle:

Without prejudice to Article 26 and Article 69 concerning translations of part I documents, the application dossier for an application limited to Part II of the assessment report referred to in Article 11 and the application dossier for an application referred to in Article 14 shall be limited to sections K to S of this Annex.

K. RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

59. Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is.

60. Where the recruitment of subjects is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings. The procedures proposed for handling responses to the advertisement shall be outlined. This includes copies of communications used to invite subjects to participate in the clinical trial and arrangements for

information or advice to the respondents found not to be suitable for inclusion in the clinical trial.

L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)

61. All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent, or other alternative means according to Article 29(1) for recording informed consent. If electronic means are used, the sponsor shall ensure that the systems used have proportionate security levels, and that safeguards regarding confidentiality are in place.

62. A description of procedures relating to informed consent for all subjects, and in particular:

(a) in clinical trials with minors or incapacitated subjects, the procedures to obtain informed consent from the legally designated representatives, and the involvement of the minor or incapacitated subject shall be described;

(b) if a procedure with consent witnessed by an impartial witness is to be used, relevant information on the reason for using an impartial witness, on the selection of the impartial witness and on the procedure for obtaining informed consent shall be provided;

(c) in the case of clinical trials in emergency situations as referred to in Article 35, the procedure for obtaining the informed consent of the subject or the legally designated representative to continue the clinical trial shall be described;

(d) in the case of clinical trials in emergency situations as referred to in Article 35, the description of the procedures followed to identify the urgency of the situation and to document it;

(e) in the case of clinical trials where their methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products, as referred to in Article 30, and where, as a consequence, simplified means for obtaining informed consent will be used, the simplified means shall be described.

(f) in case of using electronic informed consent, a description of the electronic system and the procedure to inform, obtain, document and store the informed consent.

63. In the cases set out in paragraph 62, the information given to the subject and to his or her legally designated representative shall be submitted.

M. SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)

64. A list of the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites shall be submitted.

65. Description of the qualification of the investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care shall be described.

66. Any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the investigators shall be presented.

N. SUITABILITY OF THE FACILITIES (INFORMATION PER MEMBER STATE CONCERNED)

67. A duly justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the clinical trial site or by some other responsible person, according to the system in the Member State concerned, shall be submitted.

O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)

68. Proof of insurance, a guarantee, or a similar arrangement shall be submitted, if applicable.

P. FINANCIAL AND OTHER ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

69. A brief description of the financing of the clinical trial.

70. Information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.

71. Description of any other agreement between the sponsor and the site shall be submitted.

Q. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)

72. Proof of payment shall be submitted, if applicable.

R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION

73. A statement by the sponsor or his or her representative that data will be collected and processed in accordance with Directive 95/46/EEC shall be provided.

S. ANY TRANSLATION OF DOCUMENTS FROM ANNEX Ia REQUIRED IN THE NATIONAL LANGUAGE OF THE MEMBER STATE CONCERNED in accordance with Article 26 and Article 69

This submission may include, depending on the requirements of the Member State concerned, but is not limited to, Cover Letter, Scientific synopsis, Lay summary, Labels and Patient-facing documents from Part I of the application dossier.'

ANNEX III

Annex II to Regulation (EU) 2019/6 is amended as follows:

(1) Section I.1.8 is deleted.

(2) In section IIIa.2C2.1, point (7) is deleted.

(3) Section IIIa.3A6 is amended as follows:

(i) the heading IIIa.3A6.1 is deleted

(ii) in point (1), the following paragraph is added:

'Details of the environmental risk assessment shall be provided in accordance with guidance published by the Agency. Where the environmental risks for a veterinary medicinal product have already been assessed, relevant justification for not submitting a new environmental risk assessment may be provided.'

(iii) in point (2), the first paragraph is replaced by the following:

'The environmental risk assessment shall follow a stepwise approach. The first phase shall assess the potential exposure of the environment to the product and the level of risk associated with any such exposure taking into account in particular the following items:'

(iv) in point (3), the first paragraph is replaced by the following:

'Where the conclusions of the first phase indicate a relevant potential risk for the environment, the applicant shall proceed to the second phase. In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with guidance published by the Agency. The extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the substance(s) concerned, including metabolites in case of an identified risk, which has been obtained during the conduct of the other tests and trials required by this Regulation, shall be taken into consideration.'

(v) the following point (4) is added:

'For veterinary medicinal products containing or consisting of genetically modified organisms, the following elements, which are based on the general principles laid down in Annex II to Directive 2001/18/EC, shall be addressed in the environmental risk assessment:

(a) description of the genetically modified organism, the modifications introduced and the characteristics of the finished product;[1] cross-reference to other parts of the application is acceptable.;

(b) identification and characterisation of hazards for the environment, animals and for human health;

(c) exposure characterisation assessing the likelihood or probability that the identified hazards materialise;

[1] Cross-reference to other parts of the application is possible.

(d) risk characterisation taking into account the magnitude of each possible hazard and the likelihood or probability of that adverse effect occurring;

(e) risk minimisation strategies proposed to address the identified risks.'

(vi) Section IIIa.3A6.2 is deleted.

(4) In section IIIb.2C2.1, point (5) is deleted.

(5) Section IIIb.3D is amended as follows:

(i) in point (1), the following paragraph is added:

'Details of the environmental risk assessment shall be provided in accordance with guidance published by the Agency. Where the environmental risks for a veterinary medicinal product have already been assessed, relevant justification for not submitting a new environmental risk assessment may be provided.'

(ii) in point (2), the first paragraph is replaced by the following:

'The environmental risk assessment shall follow a stepwise approach. The first phase shall assess the potential exposure of the environment to the product and the level of risk associated with any such exposure taking into account in particular the following items:'

(iii) point (5) is replaced by the following:

'For veterinary medicinal products containing or consisting of genetically organisms, the following elements, which are based on the general principles laid down in Annex II to Directive 2001/18/EC, shall be addressed in the environmental risk assessment:

(a) description of the genetically modified organism, the modifications introduced and the characteristics of the finished product; cross-reference to other parts of the application is acceptable;

(b) identification and characterisation of hazards for the environment, animals and for human health;

(c) exposure characterisation assessing the likelihood or probability that the identified hazards materialise;

(d) risk characterisation taking into account the magnitude of each possible hazard and the likelihood or probability of that adverse effect occurring

(e) risk minimisation strategies proposed to address the identified risks.'

(6) Section IIIb.3E. is deleted

(7) Section V.1.3.2 is deleted.