ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

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. Without prejudice to Article 26, 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 R of this Annex.

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;

(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 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.

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 end-points, 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.

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.

1.1. **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.

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.

1.2. **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.

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:			
— within the conditions of the SmPC	SmPC		
— outside the conditions of the SmPC	SmPC	If appropriate	If appropriate
— after modification (for example blinding)	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 product	SmPC+P+A	Yes	Yes

(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)

is supplied by the marketing authorisation holder			
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			
— is supplied by the same manufacturer	SmPC+P+A	Yes	Yes
— is supplied by another manufacturer	SmPC+S+P+A	Yes	Yes
The investigational medicinal product was subject to a previous clinical trial application and authorised in the Member State concerned and has not been modified, and			
— no new data are available since last amendment to the clinical trial application,	Reference to previous submission		
— new data are available since last amendment to the clinical trial application,	New data	New data	New data

(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)

—	is used under different conditions	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.

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.

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.

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.

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.

ANNEX II

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATION

A.INTRODUCTION AND GENERAL PRINCIPLES

1. Where a substantial modification concerns more than one clinical trial of the same sponsor and the same investigational medicinal product, the sponsor may make a single request for authorisation of the substantial modification. The cover letter shall contain a list of all clinical trials to which the application for substantial modification relates, with the EU trial numbers and respective modification code numbers of each of those clinical trials.

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

(a) the information provided is complete;

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

(c) the clinical trial will be conducted in accordance with the amended documentation.

B. COVER LETTER

3. A cover letter with the following information:

(a) in its subject line, the EU trial number with the title of the clinical trial and the substantial modification code number which allows unique identification of the substantial modification, and which shall be used consistently throughout the application dossier;

(b) identification of the applicant;

(c) identification of the substantial modification (the sponsor's substantial modification code number and date), whereby the modification may refer to several changes in the protocol or scientific supporting documents;

(d) a highlighted indication of any special issues relating to the modification and an indication as to where the relevant information or text is located in the original application dossier;

(e) identification of any information not contained in the modification application form that might impact on the risk to subjects; and

(f) where applicable, a list of all clinical trials which are substantially modified, with EU trial numbers and respective modification code numbers.

C. MODIFICATION APPLICATION FORM

4. The modification application form, duly completed.

D. DESCRIPTION OF THE MODIFICATION

5. The modification shall be presented and described as follows:

(a) an extract from the documents to be amended showing previous and new wording in track changes, as well as an extract showing only the new wording, and a explanation of the changes; and

(b) notwithstanding point (a), if the changes are so widespread or far-reaching that they justify an entirely new version of the document, a new version of the entire document (in such cases, an additional table lists the amendments to the documents, whereby identical changes can be grouped).

6. The new version of the document shall be identified by the date and an updated version number.

E. SUPPORTING INFORMATION

7. Where applicable, additional supporting information shall at least include:

(a) summaries of data;

(b) an updated overall risk/benefit assessment;

(c) possible consequences for subjects already included in the clinical trial;

(d) possible consequences for the evaluation of the results;

(e) documents which relate to any changes to the information provided to subjects or their legally designated representatives, the informed consent procedure, informed consent forms, information sheets, or to letters of invitation; and

(f) a justification for the changes sought in the application for a substantial modification.

F. UPDATE OF EU APPLICATION FORM

8. If a substantial modification involves changes to entries on the EU application form referred to in Annex I, a revised version of that form shall be submitted. The fields affected by the substantial modification shall be highlighted in the revised form.

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

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

ANNEX III

SAFETY REPORTING

1. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

1. The investigator does not need to actively monitor subjects for adverse events once the clinical trial has ended with regard to the subjects treated by him, unless otherwise provided for in the protocol.

2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) BY THE SPONSOR TO THE AGENCY IN ACCORDANCE WITH ARTICLE 42

2.1. **Adverse Events and Causality**

2. Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

3. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

4. In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

2.2. **Expectedness, unexpectedness and the RSI**

5. In determining whether an adverse event is unexpected, consideration shall be given to whether the event adds significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction.

6. The expectedness of an adverse reaction shall be set out by the sponsor in the RSI. Expectedness shall be determined on the basis of events previously observed with the active substance and not on the basis of the anticipated pharmacological properties of a medicinal product or events related to the subject's disease.

7. The RSI shall be contained in the SmPC or the IB. The covering letter shall refer to the location of the RSI in the application dossier. If the investigational medicinal product is authorised in several Member States concerned with different SmPCs, the sponsor shall select the most appropriate SmPC, with reference to subject safety, as the RSI.

8. The RSI may change during the conduct of a clinical trial. For the purpose of reporting SUSARs the version of the RSI at the moment of occurrence of the SUSAR shall apply. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 3 of this Annex.

9. If information on expectedness has been provided by the reporting investigator, this shall be taken into consideration by the sponsor.

2.3. **Information for the reporting of SUSARs**

10. The information shall at least include:

(a) a valid EU trial number;

(b) a sponsor study number;

(c) an identifiable coded subject;

(d) an identifiable reporter;

(e) a SUSAR;

(f) a suspect investigational medicinal product (including active substance name-code);

(g) a causality assessment.

11. In addition, in order to properly process the report electronically, the following administrative information shall be provided:

(a) the sender's (case) safety report unique identifier;

(b) the receive date of the initial information from the primary source;

(c) the receipt date of the most recent information;

(d) the worldwide unique case identification number;

(e) the sender identifier.

2.4. **Follow-up reports of SUSARs**

12. If the initial report of a SUSAR referred to in point (a) of Article 42(2) (fatal or life-threatening) is incomplete, for example if the sponsor has not provided all the

information within seven days, the sponsor shall submit a completed report based on the initial information within an additional eight days.

13. The clock for initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

14. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, that is the date of receipt of the new information. This information shall be reported as a follow-up report within 15 days.

15. If the initial report of a SUSAR referred to in Article 42(2)(c) (initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening) is incomplete, a follow-up report shall be made as soon as possible, but within a maximum of seven days of first knowledge of the reaction being fatal or life-threatening. The sponsor shall submit a completed report within an additional eight days.

16. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, if the initial report has not yet been submitted, a combined report shall be created.

2.5. **Unblinding treatment allocation**

17. The investigator shall only unblind the treatment allocation of a subject in the course of a clinical trial if unblinding is relevant to the safety of the subject.

18. When reporting a SUSAR to the Agency, the sponsor shall only unblind the treatment allocation of the affected subject to whom the SUSAR relates.

19. If an event is potentially a SUSAR the blind shall be broken for that subject only by the sponsor. The blind shall be maintained for other persons responsible for the ongoing conduct of the clinical trial (such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.

20. Unblinded information shall be accessible only to persons who need to be involved in the safety reporting to the Agency, to Data Safety Monitoring Boards (’DSMB’), or to persons performing ongoing safety evaluations during the clinical trial.

21. However, for clinial trials carried out in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another ’serious’ outcome, that may potentially be reported as a SUSAR, is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor shall highlight in the protocol which serious events are to be treated as disease-related and are not subject to systematic unblinding and expedited reporting.

22. If following unblinding, an event turns out to be a SUSAR the reporting rules for SUSARs set out in Article 42 and in Section 2 of this Annex shall apply.

3. ANNUAL SAFETY REPORTING BY THE SPONSOR

23. The report shall contain, in an appendix, the RSI in effect at the start of the reporting period.

24. The RSI in effect at the start of the reporting period shall serve as RSI during the reporting period.

25. If there are significant changes to the RSI during the reporting period they shall be listed in the annual safety report. Moreover, in this case the revised RSI shall be submitted as an appendix to the report, in addition to the RSI in effect at the start of the reporting period. Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period.

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

1. Clinical trial identification (including title of the trial and protocol number);

2. Identifiers (including EU trial number, other identifiers);

3. Sponsor details (including scientific and public contact points);.

4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);

5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product;

6. General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used);

7. Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).

B. SUBJECT DISPOSITION:

1. Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);

2. Pre-assignment Period;

3. Post Assignment Periods.

C. BASELINE CHARACTERISTICS:

1. Baseline Characteristics (Required) Age;

2. Baseline Characteristics (Required) Gender;

3. Baseline Characteristics (Optional) Study Specific Characteristic.

D. END POINTS:

1. End point definitions[(1)]

2. End Point #1

   Statistical Analyses

3. End Point #2

   Statistical Analyses

E. ADVERSE EVENTS:

1. Adverse events information;

2. Adverse event reporting group;

3. Serious adverse event;

4. Non-serious adverse event.

F. ADDITIONAL INFORMATION:

1. Global Substantial Modifications;

2. Global Interruptions and re-starts;

3. Limitations, addressing sources of potential bias and imprecisions and Caveats;

4. A declaration by the submitting party on the accuracy of the submitted information.

ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);

2. Name and contact details of the sponsor;

3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);

4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);

5. Investigational medicinal products used;

6. Description of adverse reactions and their frequency;

7. Overall results of the clinical trial;

8. Comments on the outcome of the clinical trial;

9. Indication if follow up clinical trials are foreseen;

10. Indication where additional information could be found.

ANNEX VI

LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

A.UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

A.1. **General rules**

1. The following particulars shall appear on the immediate and the outer packaging:

(a) name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the ’main contact’);

(b) the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance is to appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;

(c) pharmaceutical form, route of administration, quantity of dosage units;

(d) the batch or code number identifying the contents and packaging operation;

(e) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(f) the subject identification number and/or the treatment number and, where relevant, the visit number;

(g) the name of the investigator (if not included in (a) or (e));

(h) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(i) ’For clinical trial use only’ or similar wording;

(j) the storage conditions;

(k) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity; and

(l) ’Keep out of reach of children’, except when the product is for use in trials where the product is not taken home by subjects.

2. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings or handling instructions may be displayed.

3. The address and telephone number of the main contact shall not be required to appear on the label if subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times.

A.2. **Limited labelling of immediate packaging**

A.2.1. *Immediate and outer packaging provided together*

4. When the product is provided to the subject or the person administering the medicinal product in an immediate packaging and outer packaging intended to remain together, and the outer packaging carries the particulars listed in section A.1., the following particulars shall appear on the immediate packaging (or any sealed dosing device that contains the immediate package):

(a) name of the main contact;

(b) pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch and/or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number and/or the treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

A.2.2. *Small immediate packaging*

5. If the immediate packaging takes the form of blister packs or small units such as ampoules on which the particulars required in section A.1. cannot be displayed, the outer packaging provided shall bear a label with those particulars. The immediate packaging shall contain the following:

(a) name of the main contact;

(b) route of administration (may be excluded for oral solid dose forms) and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

B. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS

6. The following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) name of the medicinal product, followed by its strength and pharmaceutical form;

(c) statement of the active substances expressed qualitatively and quantitatively per dosage unit;

(d) batch or code number identifying the contents and packaging operation;

(e) clinical trial reference code allowing identification of the clinical trial site, investigator and subject;

(f) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(g) ’For clinical trial use only’ or similar wording;

(h) the storage conditions; and

(i) period of use (expiry date or retest date as applicable).

C. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;

(c) ’For clinical trial use only’ or similar wording.

D. REPLACING OF INFORMATION

8. The particulars listed in sections A, B and C, other than those particulars listed in paragraph 9, may be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

9. The particulars referred to in the following points shall not be omitted from the label of a product:

(a) paragraph 1, points (b), (c), (d), (f), (j) and (k);

(b) paragraph 4, points (b), (c), (e), and (f);

(c) paragraph 5, points (b), (c), (e), and (f);

(d) paragraph 6, points (b), (d), (e), (h), and (i).

ANNEX VII

CORRELATION TABLE

Directive 2001/20/EC	**This Regulation**
Article 1(1)	Article 1 and Article 2(1) and (2) points (1), (2) and (4)
Article 1(2)	Article 2(2) point (30)
Article 1(3), first subparagraph	—
Article 1(3), second subparagraph	Article 47, third subparagraph
Article 1(4)	Article 47, second subparagraph
Article 2	Article 2
Article 3(1)	—
Article 3(2)	Articles 4, 28, 29 and 76
Article 3(3)	Article 28(1)(f)
Article 3(4)	Article 28(1)(g)
Article 4	Articles 10(1), 28, 29 and 32
Article 5	Articles 10(2), 28, 29 and 31
Article 6	Articles 4 to 14
Article 7	Articles 4 to 14
Article 8	—
Article 9	Articles 4 to 14
Article 10(a)	Articles 15 to 24
Article 10(b)	Article 54
Article 10(c)	Articles 37 and 38
Article 11	Article 81
Article 12	Article 77
Article 13(1)	Article 61(1) to (4)
Article 13(2)	Article 61(2)
Article 13(3), first subparagraph	Articles 62(1) and 63(1) and (3)
Article 13(3), second subparagraph	Article 63(1)
Article 13(3), third subparagraph	—
Article 13(4)	Article 62
Article 13(5)	—
Article 14	Articles 66 to 70
Article 15(1)	Article 78(1), (2) and (5)

Article 15(2)	Article 78(6)
Article 15(3)	—
Article 15(4)	—
Article 15(5)	Articles 57, 58 and 78(7)
Article 16	Article 41
Article 17(1)(a) to (c)	Article 42
Article 17(1)(d)	—
Article 17(2)	Article 43
Article 17(3)(a)	—
Article 17(3)(b)	Article 44(1)
Article 18	—
Article 19, first paragraph, first sentence	Article 75
Article 19, first paragraph, second sentence	Article 74
Article 19, second paragraph	Article 92
Article 19, third paragraph	—
Article 20	—
Article 21	Article 88
Article 22	—
Article 23	—
Article 24	—

(**1**) Information shall be provided for as many end points as defined in the protocol.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) No 536/2014 of the European Parliament and of the Council.