Attachment 3: Common Technical Document Headings for Non-clinical pharmacology and toxicology data

4.2.1	Pharmacology
4.2.1.1	Primary Pharmacodynamics
4.2.1.2	Secondary Pharmacodynamics
4.2.1.3	Safety Pharmacology
4.2.1.3	Pharmacodynamic interactions
4.2.2	Pharmacokinetics
4.2.2.1	Analytical Methods and Validation Reports
4.2.2.2	Absorption
4.2.2.3	Distribution
4.2.2.4	Metabolism
4.2.2.5	Excretion
4.2.2.6	Pharmacokinetic Drug Interactions
4.2.2.7	Other Pharmacokinetic Studies
4.2.3	Toxicology:
4.2.3.1	Single Dose Toxicity
4.2.3.2	Repeat-Dose Toxicity*
4.2.3.3	Genotoxicity
4.2.3.4	Carcinogenicity *
4.2.3.5	Reproductive and Developmental Toxicity *
4.2.3.6	Local Tolerance
4.2.3.7	Other Toxicity Studies
4 2.4	Nonclinical Overview (according to information available)

* These sections should be supported by toxicokinetic evaluations

Attachment 4: Common Technical Document Headings for Clinical Data

5.3	Clinical Study Reports
5.3.1	Reports of Biopharmaceutic Studies
5.3.1.1	Bioavailability (BA) Study Reports
5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports
5.3.1.3	*In vitro-In vivo* Correlation Study Reports
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
5.3.2.1	Plasma Protein Binding Study Reports
5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies
5.3.2.3	Reports of Studies Using Other Human Biomaterials
5.3.3	Reports of Human Pharmacokinetic (PK) Studies
5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports
5.3.3.2	Patient PK and Initial Tolerability Study Reports
5.3.3.3	Intrinsic Factor PK Study Reports
5.3.3.4	Extrinsic Factor PK Study Reports
5.3.3.5	Population PK Study Reports
5.3.4	Reports of Human Pharmacodynamic (PD) Studies
5.3.4.1	Healthy Subject PD and PK/PD Study Reports
5.3.4.2	Patient PD and PK/PD Study Reports
5.3.5	Reports of Efficacy and Safety Studies
5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
5.3.5.2	Study Reports of Uncontrolled Clinical Studies
5.3.5.3	Reports of Analyses of Data from More Than One Study
5.3.5.4	Other Clinical Study Reports
5.3.6	Reports of Post-Marketing Experience
5.4.1	Literature References

Attachment 5: Headings for aspects of a trial to which a sponsor might wish to make a substantial amendment.

In all cases, an amendment is only to be regarded as "substantial" where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the patients;
- the scientific values of the trial;
- the conduct or management of the trial;
- the quality or safety of any IMP used in the trial.

The headings below are examples of aspects of a trial where amendments may need to be made, of which only some need to be notified as substantial. There may be other aspects of the trial where amendments meet the criteria for substantial.

Amendments related to the protocol

Purpose of trial
Design of trial
Informed consent
Recruitment procedure
Measures of efficacy
Schedule of samples
Addition or deletion of tests or measures
Number of participants
Age range of participants
Inclusion criteria
Exclusion criteria
Safety monitoring
Duration of exposure to the investigational medicinal product(s)
Change of posology of the investigational medicinal product(s)
Change of comparator
Statistical analysis

Amendments related to the trial arrangements

Change of the principal investigator or addition of new ones
Change of the co-ordinating investigator
Change of the trial site or addition of new sites (See section 4.2.3 on how to notify changes)
Change of the sponsor or legal representative
Change of the CRO assigned significant tasks
Change of the definition of the end of the trial

Amendments related to the IMP

Changes to investigational medicinal product quality data concerning:
Change of name or code of IMPs

Immediate packaging material
Manufacturer(s) of active substance
Manufacturing process of the active substance
Specifications of active substance
Manufacture of the medicinal product
Specification of the medicinal product
Specification of excipients where these may affect product performance
Shelf-life including after first opening and reconstitution
Major change to the formulation
Storage conditions
Test procedures of active substance
Test procedures of the medicinal product
Test procedures of non-pharmacopoeial excipients

Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment).

For example concerning:

Results of new pharmacology tests
New interpretation of existing pharmacology tests
Result of new toxicity tests
New interpretation of existing toxicity tests
Results of new interaction studies

Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment.

For example concerning:

Safety related to a clinical trial or human experience with the investigational medicinal product
Results of new clinical pharmacology tests
New interpretation of existing clinical pharmacology tests
Results of new clinical trials
New interpretation of existing clinical trial data
New data from human experience with the investigational medicinal product
New interpretation of existing data from human experience with the investigational medicinal product

Annex 1: Application Form

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request : Date of request for information to make it valid :	Date of request for additional information :	Grounds for non acceptance/ negative opinion : yes ☐ no ☐ If yes, date :
Date of valid application : Date of start of procedure:	Date of receipt of additional / amended information :	Authorisation/ positive opinion : yes ☐ no ☐ If yes, date :
Competent authority, Ethics Committee registration number :		

To be filled in by the applicant:

This form is common for request for authorisation from the Competent Authority and for the opinion from an Ethics Committee. Please indicate the relevant purpose in a box below.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: ☐

REQUEST FOR OPINION OF THE ETHICS COMMITTEE: ☐

A. TRIAL IDENTIFICATION

Member State in which the submission is being made :

EudraCT number[1] Full title of the trial : Sponsor's protocol code number, version, and date[2]: Name or abbreviated title of the trial where available:

ISRCTN number[3], if available :

[1] Append the EudraCT number confirmation receipt

[2] Any translation of the protocol should be assigned the same date and version as those in the original document.

[3] International Standard Randomised Controlled Trial Number

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B1. Sponsor
Name of organisation : Name of the person to contact: Address : Telephone number : Fax number : e-mail:

B2. Legal representative[4] of the sponsor in the Community for the purpose of this trial (if different from the sponsor)
Name of organisation: Name of the person to contact : Address : Telephone number : Fax number : e-mail:

Status of the sponsor : commercial[5] ☐ non commercial ☐

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C1. Request for the competent authority ☐	**C2. Request for the Ethics Committee** ☐

- Sponsor ☐
- Legal representative of the sponsor ☐
- Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐
  - Organisation :
  - Name of contact person :
  - Address :
  - Telephone number :
  - Fax number :
  - E-mail
	- Sponsor ☐
	- Legal representative of the sponsor ☐
	- Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐
	  - Organisation :
	  - Name of contact person :
	  - Address :
	  - Telephone number :
	  - Fax number :
	  - E-mail :
	- Investigator in charge of the application :
	  • Coordinating investigator (for multicentre trial) ☐
	  • Principal investigator (for single centre trial) ☐
	In the case of the investigator, complete below :
	  - Name :
	  - Address :
	  - Telephone number :
	  - Fax number :
	  - E-mail :

[4] : In accordance with article 19 of Directive 2001/20/EC

[5] : A commercial sponsor is a person or organisation that takes responsibility for a trial which at the time of the application is part of the development programme for a marketing authorisation of a medicinal product.

D. INFORMATION ON INVESTIGATIONAL MEDICINAL PRODUCT(S) BEING USED IN THE TRIAL : MEDICINAL PRODUCT BEING TESTED OR USED AS A COMPARATOR

Information on each 'Bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for both the medicinal product being tested and the product being used as a comparator. Information on placebo, if relevant, should be provided in section E. If the trial is performed with several investigational medicinal products (IMP), use extra pages and give each IMP a sequential number ; information should be given for each product, likewise if the product is a combination product information should be given for each active substance.

Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial(assign numbers from 1-n):

This refers to the IMP number : (.....)

IMP being tested ☐

IMP used as a comparator ☐

D.1. STATUS OF THE INVESTIGATIONAL MEDICINAL PRODUCT TO BE USED IN THE TRIAL

D.1(a) Has the IMP to be used in the trial a marketing authorisation (MA) :	Yes	No	**If yes, specify for the product to be used in the trial**		
			Trade name[6]	Name of the MA holder[6]	MA number[6]
• In the Member State concerned by this submission? - If yes to this question and if the IMP is not modified but the trade name and MA holder are not fixed in the protocol, go to D.1(b)	☐	☐			
If no to the previous question, • in another Member State from which it is sourced for this trial? - If yes specify, - in which Member State?	☐	☐			
If no to the 2 previous questions, • in a third country from which it is sourced for this trial? - If yes, in which country?	☐	☐			

[6] Available from the Summary of Product Characteristics

D.1(b) Situations where the IMP to be used in the CT has a MA in the MS concerned but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start:	Yes	No
In the protocol, is treatment defined only by active substance? - if yes, go to D2	☐	☐
In the protocol, treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS. - if yes, go to D2.	☐	☐
The products to be administered as IMPs are defined as belonging to an ATC group[6]. - if yes give the ATC group (level 3 or more to the level that can be defined) of the applicable authorised codes in the ATC code field in D.2 of this form	☐	☐
Other : - if yes, please specify :	☐	☐

Has the use of the investigational medicinal product been previously authorised in a clinical trial conducted by the sponsor in the Community?

yes ☐ no ☐

Has the investigational medicinal product been designated in this indication as an orphan drug in the Community ?

yes ☐ no ☐

If yes, give the orphan drug designation number[7] :

D.2. DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Product name where applicable[8] :

Product code where applicable[9] :

Name of each active substance (INN or proposed INN if available, specify whether proposed or approved INN) :

Other available name for each active substance (CAS, current sponsor code(s), other descriptive name, etc : provide all available) :

ATC code, if officially registered[10]:

Pharmaceutical form (use standard terms) :

Route of administration (use standard terms) :

Strength (specify all strengths to be used) :
- Concentration (number) :
- Concentration unit :
- Concentration type ("exact number", "range", "more than" or "up to").

[7] according to the Community register on orphan medicinal products (Regulation (EC) n° 141/2000) : http://pharmacos.eudra.org/F2/register/orphreg.htm

[8] In the absence of a tradename, this is the name routinely used by sponsor to identify the IMP in the CT documentation (protocol, IB...)

Type of medicinal product	
Does the investigational medicinal product contain an active substance :	
- of chemical origin ?	yes ☐ no ☐
- of biological / biotechnological origin[11]	yes ☐ no ☐
Is this :	
- a cell therapy medicinal product[11]?	yes ☐ no ☐
- a gene therapy medicinal product[11]?	yes ☐ no ☐
- a radiopharmaceutical medicinal product ?	yes ☐ no ☐
- an immunological medicinal product (such as vaccine, allergen, immune serum) [11] ?	yes ☐ no ☐
- a herbal medicinal product?	yes ☐ no ☐
- a homeopathic medicinal product?	yes ☐ no ☐
- a medicinal product containing genetically modified organisms[11] ?	yes ☐ no ☐
◦ If yes,	
▪ Has the authorisation for contained use or release been granted?	yes ☐ no ☐
▪ Or is it pending?	yes ☐ no ☐
- another type of medicinal product?	yes ☐ no ☐
◦ If yes, specify :	

D.3. BIOLOGICAL / BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS INCLUDING VACCINES

Type of product	
- Extractive	yes ☐ no ☐
- Recombinant	yes ☐ no ☐
- Vaccine	yes ☐ no ☐
- GMO	yes ☐ no ☐
- Plasma derived products	yes ☐ no ☐
- Others	yes ☐ no ☐
If others, specify :	

D.4. SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)

Origin of cells	
- autologous	yes ☐ no ☐
- allogeneic	yes ☐ no ☐
- Xenogeneic	yes ☐ no ☐
- if yes, specify species of origin :	

[9] In the absence of a tradename, this is a code designated by the sponsor which represents the name routinely used by the sponsor to identify the product in the CT documentation. This code is potentially used in the case of combinations of drugs or drugs and devices.

[10] Available from the Summary of Product Characteristics

[11] Complete also sections D3, D4 or D5

Type of cells	
- Stem cells	yes ☐ no ☐
- Differentiated cells	yes ☐ no ☐
If yes, specify the type (e.g. keratinocytes, fibroblasts, chondrocytes,...) :	
- Others :	yes ☐ no ☐
If others, specify :	

D.5. GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS

Gene(s) of interest :

In vivo gene therapy: ☐	**Ex vivo gene therapy :** ☐

Type of gene transfer product	
- Nucleic acid (e.g. plasmid) :	☐ yes ☐ no
If yes, specify	
- if naked :	☐ yes ☐ no
- or complexed :	☐ yes ☐ no
- Viral vector :	☐ yes ☐ no
If yes, specify the type : adenovirus, retrovirus, AAV, ...:	
- Others :	☐ yes ☐ no
If others, specify :	

Genetically modified cells :	☐ yes ☐ no
If yes, specify :	
- origin of the cells :	
- autologous :	☐ yes ☐ no
- allogeneic :	☐ yes ☐ no
- xenogeneic :	☐ yes ☐ no
- if yes, specify species of origin :	
- type of cells (hematopoietic stem cells, ...) :	

E. INFORMATION ON PLACEBO (if relevant) (repeat as necessary)

This refers to Placebo number: (.....)	
Is a there a placebo: ☐ yes ☐ no	
Which IMP is it a placebo for?	Specify IMP Number(s) from D
Pharmaceutical form :	
Route of administration :	
Composition, apart from the active substance(s) :	
- is it otherwise identical to the IMP?	☐ yes ☐ no
- if not, specify major ingredients :	

F. AUTHORISED SITE RESPONSIBLE FOR THE RELEASE OF THE INVESTIGATIONAL MEDICINAL PRODUCT IN THE COMMUNITY

*This section is dedicated to **finished** investigational medicinal products, i.e. medicinal products randomised, packaged, labelled and released for use in the clinical trial. If there is more than one site or more than one IMP is released, use extra pages and give each IMP its number from D or E for any placebo. In the case of multiple sites indicate the product released by each site.*

Who is responsible in the Community for the release of the finished IMP? (please tick the appropriate box) : **This site is responsible for release of (specify the number(s) from D of the IMP and E for the placebo concerned) : .....**	
- Manufacturer - Importer - Both manufacturer and importer	☐ ☐ ☐
- Name of the organisation: - Address : - Please, give the manufacturer or importer authorisation number : If no authorisation, give the reasons : - Has the site been inspected by the Community authorities? If yes, date of the last inspection:	yes ☐ no ☐

G. GENERAL INFORMATION ON THE TRIAL

Medical condition or disease under investigation	
Specify the medical condition (free text) : ICD classification code[12] : MedDRA classification code[13] : Is it a rare disease[14] ?	yes ☐ no ☐

Objective of the trial
Main objective : Secondary objectives :

Principal inclusion criteria *(list the most important)*

Principal exclusion criteria *(list the most important)*

Primary end point(s) :

[12] Source : World Health Organization

[13] The information on the ICD and MedDRA classification is optional..When both classifications are available only one should be provided; in this case applicants are encouraged to provide the MedDRA classification.

[14] Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation : COM/436/01 (www.emea.eu.int/htms/human/comp/orphaapp.htm)

Scope of the trial – Tick all boxes where applicable	
- Diagnosis	☐
- Prophylaxis	☐
- Therapy	☐
- Safety	☐
- Efficacy	☐
- Pharmacokinetic	☐
- Pharmacodynamic	☐
- Bioequivalence	☐
- Dose Response	☐
- Pharmacogenomic	☐
- Pharmacoeconomic	☐
- Others	☐
If others, specify :	☐

Trial type[15] **and phase**			
☐ Human pharmacology (Phase I) Is it: ☐ First administration to humans ☐ Bioequivalence study ☐ Other : Please specify :	☐ Therapeutic exploratory (Phase II)	☐ Therapeutic confirmatory (Phase III)	☐ Therapeutic use (Phase IV)

Design of the trial					
Randomised :	yes ☐ no ☐				
Controlled :	yes ☐ no ☐	• If yes, specifiy :			
		Open :	Yes ☐ no ☐		
		Single blind :	Yes ☐ no ☐	Double blind :	yes ☐ no ☐
		Parallel group :	Yes ☐ no ☐	Cross over :	yes ☐ no ☐
		Other :	Yes ☐ no ☐	If yes, specify :	
		• Specify the comparator :			
		- (an) other medicinal product(s)			yes ☐ no ☐
		- placebo			yes ☐ no ☐
		- other			yes ☐ no ☐
		If yes, specify :			
Single site (see also section I) :	yes ☐ no ☐				
Multiple site (see also section I) :	yes ☐ no ☐				
Multiple Member States :	yes ☐ no ☐				
Does this trial involve third countries ?	yes ☐ no ☐				

Maximum duration of treatment of a subject according to the protocol :

Maximal dose allowed (specify : per day or total) :

Definition of the end of trial and justification, in the case where it is not the last visit of the last subject undergoing the trial :[16]

Initial estimate of the duration of the trial[17]**(years and months):**

- in the MS concerned	years	months
- in all countries concerned by the trial	years	months

[15] according to page 5 of Community guideline CPMP/ICH/291/95

H. POPULATION OF TRIAL SUBJECTS

Age			
Age span	☐ Less than 18 years If yes specify: ☐ In Utero ☐ Preterm Newborn Infants (up to gestational age ≤ 37 weeks) ☐ Newborn (0-27 days) ☐ Infant and toddler (28 days - 23 months) ☐ Children (2-11 years) ☐ Adolescent (12-17 years)	☐ Adult (18-65 years)	☐ Elderly (> 65 years)
Gender			
☐ Female	☐ Male		

Population of trial subjects		
Healthy volunteers	yes ☐	no ☐
Patients	yes ☐	no ☐
Specific vulnerable populations		
- women of child bearing potential	yes ☐	no ☐
- pregnant women	yes ☐	no ☐
- nursing women	yes ☐	no ☐
- emergency situation	yes ☐	no ☐
- subjects incapable of giving consent personally	yes ☐	no ☐
	If yes, specify :	
- others :	yes ☐	no ☐
	If yes, specify :	

Planned number of subjects to be included :
- in the Member State
For a multinational trial:
- in the Community
- in the whole clinical trial

Plans for treatment or care after the subject has ended the participation in the trial[18] (if it is different from the expected normal treatment of that condition) :
Please specify :

I. PROPOSED CLINICAL TRIAL SITES IN THE MEMBER STATE CONCERNED BY THIS REQUEST

I.1 Co-ordinating investigator (*for multicentre trial*) and principal investigator (*for single centre trial*)			
Name	Surname	Qualification (MD.....)	Address

[16] if not provided in the protocol
[17] from the 1st inclusion until the last visit of the last subject
[18] if not already provided in the protocol

I.2. Principal investigators *(for multicentre trial ; where necessary, use other forms)*			
Name	Surname	Qualification (MD.....)	Address of the principal investigator site

I.3.Central technical facilities to be used in the conduct of the trial (laboratory or other technical facility), in which the measurement or assessment of the main evaluation criteria are centralised (repeat as needed for multiple organisations)
Organisation: Name of contact person : Address : Telephone number : Duties subcontracted :

I.4. Organisations to whom the sponsor has transferred trial related duties and functions (repeat as needed for multiple organisations)
Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party? yes ☐ no ☐
If yes, specify : Organisation : Name of contact person : Address : Telephone number : Duties / functions subcontracted :

J. COMPETENT AUTHORITY / ETHICS COMMITTEE IN THE MEMBER STATE CONCERNED BY THIS REQUEST

If this application is addressed to the competent authority, please tick the Ethics Committee box and give information on the Ethics committee concerned and viceversa **Competent authority** ☐ **Ethics Committee** ☐			
Name and address : Date of submission : Authorisation/ opinion :	☐ to be requested	☐ pending	☐ given
If given, specify:	Date of authorisation / opinion: ☐ authorisation accepted / opinion favourable: ☐ not accepted / not favourable. If not acceptable / not favourable, give : - the reasons - the eventual anticipated date of resubmission :		

L. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

I hereby confirm that /confirm on behalf of the sponsor that (delete which is not applicable)

- the above information given on this request is correct
- the trial will be conducted according to the protocol, national regulation and the principles of good clinical practice
- it is reasonable for the proposed clinical trial to be undertaken.
- I will submit a summary of the final study report to the competent authority and the ethics committee concerned within a maximum 1 year deadline after the end of the study in all countries.
- I will declare the effective date of the commencement[19] of the trial to the competent authority and Ethics Committee concerned as soon as available.

APPLICANT of the request for the competent authority(as stated in section C1) :	APPLICANT of the request for the Ethics committee (as stated in section C2) :
Date : Signature : Print name:	Date : Signature : Print name:

[19] inclusion of the 1st patient in the Member State (the inclusion starts with the informed consent signature)

K. CHECK LIST OF THE INFORMATION APPENDED TO THE APPLICATION FORM

(Information that each Member State's CA and Ethics Committees require according to the table in Attachment 1)

EC CA[20]

☐ o Receipt of confirmation of EudraCT number
☐ o Covering letter
☐ o Application form
☐ o Disk with XML file for EudraCT
☐ o Protocol with all current amendments
☐ o Investigator's brochure
☐ o Investigational Medicinal Product Dossier (IMPD)
☐ o Simplified IMPD for known products
☐ o Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)
☐ o List of Competent Authorities in the Community to which the application has been submitted and details of decision
o o Copy of Ethics Committee opinion in the MS concerned where available

ADDITIONAL INFORMATION FOR SPECIAL SITUATIONS

☐ o If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor
☐ o Copy of authorisation for contained use or release of genetically modified organisms (when applicable and available)

ADDITIONAL INFORMATION ACCORDING TO MEMBER STATE REQUIREMENTS

(Attachment 1 shows the information that each Member State's CA and ethics committees require)

Subject related

☐ o Informed consent form
☐ o Subject information leaflet
☐ o Arrangements for recruitment of subjects

Protocol related

☐ o Summary of the protocol in the national language
☐ o Outline of all active trials with the same IMP
☐ o Peer review of the trial when available
☐ o Ethical assessment made by the principal/co-ordinating investigator

IMP related

☐ o Viral safety studies
☐ o Examples of the label in the national language
☐ o Applicable authorisations to cover trials or products with special characteristics (if available) eg GMO, radiopharmaceuticals products
☐ o TSE Certificate when applicable
☐ o Declaration of GMP status of active biological substance
☐ o Copy of the manufacturer authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization if the IMP is manufactured in the EU
☐ o Declaration of the qualified person that the manufacturing site works in compliance with EU GMP (when applicable)
☐ o Copy of the importer authorization as referred to in Art. 13.1. of the Directive
☐ o Certificate of analysis for test product in exceptional cases : where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected

Facilities and staff related

☐ o Facilities for the trial
☐ o CV of the coordinating investigator in the MS concerned (for multicentre trials)
☐ o CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)
☐ o Information about the supporting staff
☐ o Information on the contact person as referred to in Art 3.4 of the Directive (to be provided in the patient information sheet)

Finance related

☐ o Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial
☐ o Any insurance or indemnity to cover the liability of the investigator and sponsor
☐ o Compensation to investigators
☐ o Compensation to subjects
☐ o Agreement between sponsor and trial sites
☐ o Certificate of agreement between sponsor and investigator when not in the protocol
☐ o Agreement between the investigators and the trial sites

[20] Tick all boxes to show information provided to the ethics committee concerned (EC) and the competent authority (CA).

Annex 2: Notification of Amendment Form

REQUEST FOR AUTHORISATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request :	Grounds for non acceptance/ negative opinion : yes ☐ ☐ no If yes, date :
Date of start of procedure:	Authorisation/ positive opinion : yes ☐ ☐ no Date :
Competent authority/Ethics committee registration number of the trial :	

To be filled in by the applicant:

This form is common for request for authorisation from the Competent Authority and for the opinion from an Ethics Committee. Please indicate the relevant purpose in a box.

Member state in which the amendment is being submitted:

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: ☐

REQUEST FOR OPINION OF THE ETHICS COMMITTEE: ☐

NOTIFICATION FOR INFORMATION ONLY:

- to the competent authority ☐
- to the Ethics committee ☐

A 1.TRIAL IDENTIFICATION (When the amendment concerns more than one trial, repeat this form as necessary.)

Eudract number:

Full title of the trial :

Sponsor's protocol code number, version, and date:

A 2. AMENDMENT IDENTIFICATION

Amendment to 'protocol' ☐ If checked specify sponsor's amendment code number, version, date:

Amendment to 'initial request for authorisation' ☐ If checked specify sponsor's amendment code number, version, date:

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B 1. Sponsor
Organisation: Name of person to contact: Address : Telephone number : Fax number : e-mail:

B 2. Legal representative [2] of the sponsor in the Community for the purpose of this trial (if different from the sponsor)
Organisation: Name of person to contact: Address : Telephone number : Fax number : e-mail:

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C1. Request for the competent authority ☐	**C2. Request for the Ethics Committee** ☐

- Sponsor ☐
- Legal representative of the sponsor ☐
- Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐
- Organisation :
- Name of person to contact :
- Address :
- Telephone number :
- Fax number :
- E-mail
	- Sponsor ☐
	- Legal representative of the sponsor ☐
	- Person or organisation authorised by the sponsor to make the application. In that case, complete below: ☐
	- Organisation :
	- Name of person to contact:
	- Address :
	- Telephone number :
	- Fax number :
	- E-mail :
	- Investigator in charge of the application :
	  - Coordinating investigator (for multicentre trial) ☐
	  - Principal investigator (for single centre trial) ☐
	In the case of the investigator, complete below :
	- Name :
	- Address :
	- Telephone number :
	- Fax number :
	- E-mail :

[2] :as stated in article 19 of Directive 2001/20/EC

D. TYPE OF AMENDMENT (please tick the appropriate box)

This amendment concerns mainly urgent safety measures already implemented	*yes* ☐ no ☐
Reasons for the amendment:	
Changes in safety or integrity of trial subjects	*yes* ☐ no ☐
Changes in interpretation of scientific documents/value of the trial	*yes* ☐ no ☐
Changes in quality of IMP(s)	*yes* ☐ no ☐
Changes in conduct or management of the trial	
Change or addition of site, principal investigator(s), co-ordinating investigator	*yes* ☐ no ☐
Change of sponsor, legal representative, applicant	*yes* ☐ no ☐
Change in transfer of major trial related duties	*yes* ☐ no ☐
If yes, specify:	
Other change	*yes* ☐ no ☐
If yes, specify	
Other case	*yes* ☐ no ☐
If yes, specify	

Content of the amendment:	
an amendment to information in the application form	*yes* ☐ no ☐
an amendment to the protocol	*yes* ☐ no ☐
an amendment to other appended documents	*yes* ☐ no ☐
If yes, specify :	
Other case	*yes* ☐ no ☐
If yes, specify	

E. REASONS FOR AMENDMENT (one or two sentences):

F. BRIEF DESCRIPTION OF THE CHANGES:

G. LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

- ☐ **Covering letter stating the type of amendment and the reason(s)**
- ☐ **Summary of the proposed amendment**
- ☐ **List of modified documents (identity, version, date)**
- ☐ **If applicable, pages with previous and new wording**
- ☐ **Supportive information**
- ☐ **When applicable, revised XML file and copy of initial application form with amended data highlighted**

I. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

<table>
<tr><td colspan="2">I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable)
- the above information given on this request is correct
- the trial will be conducted according to the protocol, national regulation and the principles of good clinical practice
- it is reasonable for the proposed amendment to be undertaken.</td></tr>
<tr><td>APPLICANT of the request for the competent authority(as stated in section C1) :
Date :

Signature :

Print name :</td><td>APPLICANT of the request for the Ethics committee (as stated in section C2) :
Date :

Signature :

Print name :</td></tr>
</table>