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Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

**on clinical trials on medicinal products for human use, and repealing Directive
2001/20/EC**

(Text with EEA relevance)

{SWD(2012) 200 final}
{SWD(2012) 201 final}

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE PROPOSAL

Clinical trials as defined in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use¹ are investigations of medicines in humans where the medicines are applied outside normal clinical practice on the basis of a research protocol.

Clinical trials are performed in many different contexts. Applications for marketing authorisation and publications in medical journals are based on data generated in clinical trials. Therefore, clinical trials are an indispensable part of clinical research which, in turn, is essential to develop medicinal products and improve medical treatment. Without clinical trials, there would be no new medicines, no further development of existing medicines, and no evidence-based improvement of treatments with medicines.

In the EU/EEA, approximately 4400 clinical trials are applied for every year.² Approximately 60% of clinical trials are sponsored by the pharmaceutical industry and 40% by other stakeholders, such as academics.

Approximately 24% of all clinical trials applied for in the EU are multinational clinical trials, i.e. clinical trials intended to be performed in at least two Member States. While this seems a relatively small proportion, these 24% clinical trials involve approximately 67% of all subjects enrolled in a clinical trial. This means that, on average, a clinical trial with more than 40 subjects is conducted in more than one Member State. Mono-national clinical trials are limited to small studies with low recruitment targets.

Directive 2001/20/EC has brought about important improvements in the safety and ethical soundness of clinical trials in the EU and in the reliability of clinical trials data. However, the Clinical Trials Directive is arguably the most heavily criticised piece of EU-legislation in the area of pharmaceuticals. This criticism is voiced by all stakeholders - patients, industry, and academic research.

The data available support these criticisms:

- The number of applications for clinical trials fell by 25% from 2007 to 2011.³
- The costs for conducting clinical trials have increased. Compared to the situation prior to the application of the Directive 2001/20/EC, the staff needs for industry sponsors to handle the clinical trial authorisation process have doubled (107%); with small companies facing an even sharper increase. For non-commercial sponsors, the increase in administrative requirements due to the Directive 2001/20/EC has led to a

¹ OJ L 121, 1.5.2001, p. 34.

² Based on the figures for 2010.

³ The decrease has been 12% from 2007 to 2010.

98% increase in administrative costs. In addition, since implementation of the Directive 2001/20/EC, insurance fees have increased by 800 % for industry sponsors.

- The average delay for launching a clinical trial has increased by 90 % to 152 days.

It would be wrong to attribute the fall in clinical trial activity solely and exclusively to the Directive 2001/20/EC. However, the Directive 2001/20/EC has had many direct effects on the cost and feasibility of conducting clinical trials which, in turn, have led to a decline in clinical trial activity in the EU. Moreover, other causes (such as salary costs and the need to conduct multinational studies to reach recruitment targets) have been aggravated through regulatory requirements and consequential costs of the Directive 2001/20/EC.

Thus, the existing provisions of Directive 2001/20/EC appear to have hampered the conduct of clinical trials in Europe. It is therefore necessary for the Commission to act.

2. RESULTS OF CONSULTATIONS WITH THE INTERESTED PARTIES AND IMPACT ASSESSMENT

In preparation of the impact assessment for this proposal, the Commission held two public consultations, the first from 9 October 2009 to 8 January 2010 and the second from 9 February to 13 May 2011.

In both public consultations, all the ‘General principles and minimum standards for consultation of interested parties by the Commission’ were met. The Commission has published the responses, and a summary of them.

In addition, since 2009 the Commission has held several meetings with stakeholders to hear their assessment of how the Clinical Trials Directive is working and to discuss the impact of potential policy options. A large stakeholder workshop was held on 31 March 2011 to clarify various points put forward in the concept paper submitted to public consultation.

The Commission conducted an impact assessment in accordance with its impact assessment guidelines and published the results in an impact assessment report.

3. LEGAL ASPECTS OF THE PROPOSAL

3.1. SCOPE (CHAPTERS 1 AND 2 OF THE PROPOSED REGULATION)

The scope of the proposed Regulation is essentially identical to that of Directive 2001/20/EC. The scope is limited to clinical research on medicinal products, but it is very wide in that it only excludes clinical studies that do not involve an ‘intervention’ (e.g. surveys amongst medical practitioners without additional intervention or ‘data mining’). For ‘non-interventional studies’ which are post-authorisation safety studies initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed by the competent authority for marketing authorisations, the rules are set out in Directive 2001/83/EC

of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use⁴.

3.2 AUTHORISATION PROCEDURE AND AUTHORISATION DOSSIER (SUBMISSION, ASSESSMENT, DECISION; CHAPTERS 2, 3, 14 AND 15 OF THE PROPOSED REGULATION)

The proposal introduces a new authorisation procedure for clinical trials based on the following concepts:

- A harmonised authorisation dossier, partly codifying the existing Commission guidance contained in EudraLex, Volume 10;
- A ‘single portal’ to submit an application for conducting a clinical trial linked to an EU database. This portal is managed by the European Commission and is free of charge for sponsors;
- A flexible and swift assessment procedure without establishing a new, central bureaucracy. This assessment is largely controlled by Member States. All Member States in which the sponsor intends to conduct the clinical trial are involved in the assessment;
- A clear mechanism to appoint a ‘reporting Member State’;
- Clear timelines with a concept of tacit approval in order to ensure compliance;
- A coordination and advisory forum to address issues which may arise in the authorisation procedure. This forum is managed and chaired by the Commission;
- A clear distinction between aspects where Member States cooperate in the assessment and aspects of an intrinsic ethical or national/local nature where the assessment is made by each Member State individually;
- The option, in certain well-defined cases, for a Member State to ‘opt-out’ of the conclusions of an assessment of an application for conducting a clinical trial (‘qualified opt-out’);
- It is left to each Member State to define the organisational setup and internal competences for assessing clinical trial authorisations, provided that international guidelines on the independence of the assessors are observed;
- A swift procedure to ‘extend’ a clinical trial to additional Member States;
- Where a clinical trial is modified after it has been authorised, this modification is subject to authorisation if, and only if, the modification has a substantial

⁴ OJ L 311, 28.11.2001, p. 67.

impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

A crucial element of the rules for authorisation of a clinical trial is the clear distinction between aspects where Member States shall cooperate in the assessment of the application for authorisation of a clinical trial (Article 6 of the proposed Regulation) and those aspects where Member States conduct their assessment individually (Article 7 of the proposed Regulation). The latter includes aspects which are of an intrinsically national (for example, liability), ethical (for example, informed consent), or local (for example suitability of the clinical trial site) nature.

However, this distinction is without any prejudice as to the body which, in a Member State, performs the assessment. The proposal does not interfere with the Member State's internal organisation of the bodies involved in authorising (or not) a clinical trial. It is left to Member States to define the organisational set-up to comply with the authorisation procedure of this Regulation.

As a consequence, the proposed Regulation does not, unlike Directive 2001/20/EC, establish which body or bodies *within* a Member State approves (or not) a clinical trial. The proposed Regulation does hence not regulate or harmonise the precise functioning of Ethics Committees, impose a systematic cooperation at an operational level between Ethics Committees in the EU, or limit the Ethics Committee's scope of the assessment to genuinely-ethical issue (science and ethics cannot be separated).

Rather, the proposal leaves it up to Member States to organise, internally, the attribution of tasks to different bodies. Indeed, what matters is that Member States ensure an independent, high-quality assessment within the timelines as set out in the legislation. Moreover, it is critical to ensure clarity as to what issues are addressed in cooperation between Member States, and the issues which are addressed individually by each Member States because of their intrinsically national, local or ethical character.

In pursuing this approach, however, the proposed Regulation maintains that any application of a clinical trial will have to be assessed jointly by a reasonable number of persons who are independent, who have collectively the necessary qualifications and experience in all relevant fields, including the view of lay persons. The proposal thus stays in tune with international guidance and ensures a thorough, independent, and high quality of the assessment of an application for a clinical trial throughout the EU, without trespassing on Member States' competencies to organise their internal decision-making on an application for authorisation of a clinical trial.

3.3. INTERFACE WITH 'SCIENTIFIC ADVICE'

Independently of the regulation of clinical trials, regulators may be involved in the preparatory phase of a trial in the context of protocol assistance⁵, the paediatric

⁵ Article 6(1) of Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

investigation plan⁶, scientific advice⁷, and post-authorisation safety/efficacy studies⁸ (hereinafter referred to as 'scientific advice').

The proposed Regulation does not 'mix' the aspect of scientific advice with that of a clinical trial authorisation for two reasons:

- The involvement of the regulator in the context of scientific advice is conceptually an entirely different matter than the authorisation of a clinical trial: while the former establishes which clinical data are *desirable* in order to possibly grant or uphold a marketing authorisation at a later stage, the latter establishes if a clinical trial is *acceptable* in view of patient rights and safety, as well as data reliability and robustness. Indeed, it is perfectly conceivable (and has occasionally happened in the past) that these two approaches come to conflicting results: while, from the point of view of a future successful marketing authorisation, it may be desirable to obtain certain clinical data on the basis of experiments on humans, those clinical trials may not be acceptable from the point of view of subject protection.
- Clinical trial legislation in the EU addresses clinical trials in the abstract, i.e. independently from whether the results are intended to be used in a future marketing authorisation application, or for any other purpose (e.g. improvement of treatment strategies, comparing treatment with different medicines, etc.). This difference is usually discussed under the pattern 'commercial' vs. 'academic' clinical trials. The latter form approximately 40% of clinical trials applied for in the EU. Therefore, the concept of 'mixing' scientific advice and the clinical trials authorisation would not be workable for more than one third of all clinical trials. It is in particular these 'academic' clinical trials, however, which the proposal wants to stimulate.

3.4. PROTECTION OF SUBJECTS AND INFORMED CONSENT (CHAPTER 5 OF THE PROPOSED REGULATION)

In line with Article 3(2)a of the Charter of Fundamental Rights of the EU any intervention in the field of medicine and biology can not be performed without free and informed consent of the person concerned. The EU law has to comply with this principle. The rules on the protection of subjects and on free and informed consent had been discussed extensively in the legislative process leading to Directive 2001/20/EC. The proposed Regulation does not, with the exception of the issue of clinical trials in emergency situations (see paragraph below), change the substance of these rules. However, in terms of drafting, for the sake of clarity some provisions are re-arranged and, where possible, shortened. For example, provisions related to the

⁶ Article 15 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatrics use (OJ L 378, 27.12.2006, p. 1).

⁷ Article 56(3) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

⁸ Article 21a(b)(f) of Directive 2001/83/EC.

authorisation procedure have been moved to chapters 2 and 3 of the proposed Regulation, and provisions related to damage compensation have been moved to Chapter 12 of the proposed Regulation.

Regarding clinical trials in emergency situations, Directive 2001/20/EC does so far not address the specific situation where, because of the urgency of the situation, it is impossible to obtain free and informed consent from the subject or the legal representative ('clinical trials in emergency situations'). To address this, specific provisions on clinical trials in emergency situations have been added in line with existing international guidance documents on this issue.

Moreover as regards the protection of personal data, provisions of Directive 95/46/EC⁹ and Regulation (EC) No 45/2001¹⁰ apply.

No personal data of data subjects participating in a trial will be collected in the EU database.

It is important that personal data of investigators, which may be collected in the EU database, are kept in accordance with the exception foreseen in Article 17(3) (b) of the proposal for a regulation of the European Parliament and the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). In case of detection of cases of misconduct in a clinical trial it would be important, for example, to trace all the clinical trials in which the same investigators were involved, even several years after these clinical trials have ended.

3.5. SAFETY REPORTING (CHAPTER 7 OF THE PROPOSED REGULATION)

The rules on safety reporting follow the principles of the applicable international guidance documents. Compared to Directive 2001/20/EC, the rules have been streamlined, simplified and modernised as follows:

- The option to exclude reporting by the investigator to the sponsor of adverse events, if this is provided for in the protocol;
- Direct reporting of suspected unexpected serious adverse reactions by the sponsor to the European database EudraVigilance;
- Simplified submission of the annual safety report by the sponsor. Moreover, the annual safety report is not submitted for authorised investigational medicinal products that are used within their authorised indication. For these products, the normal pharmacovigilance rules apply.

Details of the rules on safety reporting, which codify in parts existing Commission guidance¹¹ are contained in an annex to the proposed Regulation. This will facilitate

⁹ OJ L 281, 23.11.1995, p. 31.

¹⁰ OJ L 8, 12.1.2001, p. 1.

¹¹ OJ C172, 11.6.2011, p. 1.

updating the existing rules, by way of delegated acts, in view of technical progress or global regulatory alignment.

Regarding the European database EudraVigilance, this database exists already for the purposes of pharmacovigilance activities in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 and is maintained and managed by the European Medicines Agency. Directive 2001/20/EC had already referred to this database and to the European Medicines Agency's role in administering it. The proposed Regulation does not introduce any changes in this respect.

3.6. CONDUCT OF THE TRIAL (CHAPTER 8 OF THE PROPOSED REGULATION)

Directive 2001/20/EC contains relatively few rules on the actual conduct of trials. These rules are partly contained in Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products¹², and partly contained in Commission guidance documents. The proposed Regulation brings together these rules.

3.7. INVESTIGATIONAL AND AUXILIARY MEDICINAL PRODUCTS, MANUFACTURING, LABELLING (CHAPTERS 9 TO 10 OF THE PROPOSED REGULATION)

Medicinal products intended for research and development trials are excluded from the scope of Directive 2001/83/EC, including the rules on manufacturing, importation and labelling. The rules are contained in Directive 2001/20/EC, Directive 2005/28/EC and in Commission guidelines.

The proposed Regulation brings together these rules. The new rules continue to build on the concept of 'investigational medicinal product'. However, the proposed new rules reflect more clearly the fact that investigational medicinal products may be authorised, i.e. they have already been placed on the market in accordance with Directive 2001/83/EC.

Moreover, experience with the application of Directive 2001/20/EC shows the need for clarity on medicines used in the context of a clinical trial that are not investigational medicinal products. These 'auxiliary medicinal products' (so far referred to in implementing Commission guidelines as 'non-investigational medicinal products') will be subject to proportionate rules on manufacturing and labelling.

¹² OJ L 91, 9.4.2005, p. 13.

3.8. SPONSORS, CO-SPONSORSHIP, EU CONTACT PERSON (CHAPTER 11 OF THE PROPOSED REGULATION)

Every clinical trial must have a ‘sponsor’, i.e. a legal or natural person responsible for initiating and managing the clinical trial.

This ‘responsibility’ must not be confused with issues of ‘liability’ for harm of a patient. The rules on liability depend on the applicable national liability laws and are independent from the responsibility of a sponsor.

Regarding ‘responsibility’, it is clearly preferable to have only one sponsor per clinical trial. A ‘single sponsor’ is the best means to ensure that all information regarding the entire clinical trial are provided to the bodies supervising the clinical trial and all necessary measures are taken.

However, clinical trials are increasingly initiated by loose networks of scientists or scientific institutions within one Member State or across several Member States. These networks have in some cases, for practical or legal reasons, difficulties in establishing who amongst them would act as ‘single sponsor’. These networks may also have practical or legal difficulties in forming, jointly, one legal entity to act as ‘single sponsor’.

To address this difficulty, while ensuring that the effective supervision of a clinical trial is not compromised, the proposed Regulation introduces the concept of ‘co-sponsorship’. At the outset, all co-sponsors are responsible for the entire clinical trial. However, the proposed Regulation allows co-sponsors to ‘split’ the responsibility for the clinical trials amongst themselves. Even if co-sponsors split responsibilities, however, all co-sponsors remain responsible for establishing a sponsor who can take measures requested by a Member State, and who can give information on the clinical trial as a whole.

The sponsor’s obligations are independent from where the sponsor is established — whether in the EU or in a third country. However, if the sponsor is established in a third country, in order to ensure an effective supervision of a clinical trial, an EU contact person must be provided. Communication with that contact person is considered as communication with the sponsor.

3.9. COMPENSATION FOR DAMAGES (CHAPTER 12 OF THE PROPOSED REGULATION)

Directive 2001/20/EC introduced an ‘obligatory insurance/indemnity’. This obligatory insurance/indemnity has substantially increased the costs and administrative burden of conducting clinical trials, but there is no evidence that the number of damages, or the amount, has increased with the entry into force of the Directive.

The proposed Regulation acknowledges that clinical trials do not in all cases pose an additional risk to subjects compared to treatment in normal clinical practice. Consequently, where there is no additional risk, or where that additional risk is negligible, it is not necessary to provide a specific damage compensation (be it an insurance or an indemnification) for the clinical trial. In these cases, the insurance

coverage of the medical practitioner, the institution, or product liability insurance provides sufficient coverage.

In cases where a clinical trial *does* pose an additional risk, the proposed Regulation obliges the sponsor to ensure compensation – be it through insurance, or through an indemnification mechanism. Regarding the latter, the proposed Regulation puts Member States under an obligation to set up a national indemnification mechanism which works on a not-for-profit basis. This shall help in particular 'non-commercial sponsors' to obtain coverage for possible compensations. These non-commercial sponsors have had, since the introduction of the 'obligatory insurance/indemnity' with Directive 2001/20/EC, great difficulties to obtain compensation coverage.

3.10. INSPECTIONS (CHAPTER 13 OF THE PROPOSED REGULATION)

The provisions on inspections are largely based on Directive 2001/20/EC. Regarding inspection capacity, the proposed Regulation provides the legal basis for Commission staff to perform controls in Member States and in third countries in the context of the EU *acquis* for medicinal products for human use and clinical trials.

3.11. REPEALS AND ENTRY INTO FORCE (CHAPTER 19 OF THE PROPOSED REGULATION)

The proposed Regulation addresses the aspects regulated in Directive 2001/20/EC. That Directive is therefore repealed.

In order to allow for a smooth transition from the rules of the (transposed) Directive 2001/20/EC to this Regulation, both sets of rules will apply in parallel for three years after the date of application of this Regulation. This will facilitate the transition, in particular for aspects of the authorisation procedure.

3.12 SIMPLIFICATION OF SUBSTANTIAL RULES FOR CLINICAL TRIALS WITH AUTHORISED MEDICINAL PRODUCTS AND LOW-INTERVENTION CLINICAL TRIALS

The regulation of clinical trials addresses two distinct risks: the risk to subject safety and the risk to data reliability. The former can vary widely, depending on a range of factors, in particular:

- The extent of knowledge and prior experience with the investigational medicinal product (in particular, whether or not the investigational medicinal product is authorised in the EU); and
- The type of intervention (which can range from a simple blood sample to a sophisticated biopsy).

The Directive 2001/20/EC is being heavily criticised for not taking sufficiently into account these differences in risk. Instead, the obligations and restrictions laid down in the Directive 2001/20/EC apply largely irrespectively of the risk to subject safety.

This aspect is discussed extensively in the impact assessment report. On the basis of this impact assessment, throughout the proposed Regulation aspects of risk-proportionality have been carefully taken into account.

3.13. LEGAL FORM OF A REGULATION

The proposed legal text takes the form of a Regulation and replaces the Directive 2001/20/EC.

The legal form of a Regulation ensures a coherent procedure for submission of applications for authorisations of clinical trials and their substantial modifications.

Indeed, experience shows the difficulties that are created if Member States, in their cooperation, base their work on 'similar, but different' transposing national laws. Only the legal form of a Regulation ensures that the Member States base their assessment of an application for authorisation of a clinical trial on an identical text, rather than on diverging national transposition measures.

The above holds not only for the entire authorisation process, but also for all other issues addressed in this Regulation, such as safety reporting during clinical trials, and the requirements for labelling of the medicinal products used in the context of a clinical trial.

Moreover, experience has shown that Member States misused the transposition process in order to introduce additional procedural requirements.

Finally, the legal form of a Regulation has an important simplification effect. The replacing of transposition measures at national level allows the relevant actors to plan and conduct the clinical trial, including multi-national clinical trials, on the basis of one regulatory framework, rather than on the basis of a 'patchwork' of 27 national frameworks in the transposing Member States laws.

Despite the legal form of a Regulation, however, there remain areas where the regulatory framework at EU level will be complemented by national laws: Examples are the rules on establishing who is a 'legal representative' of the subject, as well as the substantial rules of liability in the case of damages.

3.14. COMPETENCES, DOUBLE LEGAL BASIS AND SUBSIDIARITY

The proposed Regulation is, like Directive 2001/20/EC, based on Article 114 of the Treaty on the Functioning of the European Union (TFEU). In addition, the proposed Regulation is based on Article 168(4)(c) TFEU.

The proposed Regulation is based on Article 114 TFEU as it aims to harmonise the regulatory framework for clinical trials. In addition, the proposed Regulation aims to contributing to the harmonisation of the rules for pharmaceutical products placed on the market, including authorisation of their placing on the market. Finally, the proposed Regulation aims to harmonise the rules for medicines used in the context of a clinical trial, thus allowing for their free movement within the Union.

Regarding the harmonisation of the rules on clinical trials, practically every larger clinical trial is conducted in more than one Member State. Moreover, the results generated in a clinical trial may be used as basis for other clinical trials. In this respect, it is critical to ensure that the rules for patient rights and safety and data reliability and robustness are harmonised in order for them to be recognised throughout the Union.

Regarding the harmonisation of the rules for medicinal products in general, harmonised rules on clinical trials open up the possibility of referring to the results and findings of clinical trials in applications for an authorisation for placing a medicinal product on the Union market, including subsequent variations and extensions of the marketing authorisation.

Regarding the harmonisation of rules for medicinal products used in the context of a clinical trial, it has to be recalled that medicinal products intended for research and development trials are excluded from the Community Code for medicinal products for human use. Such medicinal products, however, may be produced in a different Member State from that where the clinical trial is conducted. Thus, these products do not benefit from secondary Union law ensuring their free movement while maintaining a high level of protection of human health.

In addition, the proposed Regulation is based on Article 168(4)(c) TFEU as it aims at setting high standards of quality and safety for medicinal products. According to Articles 168(4) and 4(2)(k) TFEU this Union competence is – like Article 114 TFEU - a shared competence which is exercised with the adoption of the proposed Regulation.

The proposed Regulation aims at setting high standards of quality and safety for medicinal products in two respects:

- It ensures that data generated in clinical trials is reliable and robust, thus ensuring that treatments and medicines which are supposed to be 'safer' for the patient build on reliable and robust clinical data. Only if the data on which these decisions are taken is reliable and robust, regulators, scientists, industry and the public can take the right decisions to ensure a high standard of quality and safety of medicinal products. The provisions ensuring this relate in particular to the authorisation procedure, to the rules on the conduct of the clinical trial, including the rules on monitoring and supervision by Member States.
- It aims at setting high standards to ensure the quality and safety of medicines administered to subjects in the context of a clinical trial (while acknowledging that this assurance is only possible within the limitations of the absence of knowledge, which characterises a clinical trial): This is ensured *inter alia* through the authorisation procedure set up with the proposed Regulation, as well as the rules on manufacturing of medicinal products used in the context of a clinical trials, safety reporting, and inspections.

Article 168(4)(c) TFEU cannot serve as sole legal basis, but needs to be complemented with the legal basis of Article 114 TFEU for the following reasons:

- As set out above, the proposed Regulation pursues equally as object the establishment and functioning of the internal market, and the setting of high standards of quality and safety for medicinal products;
- The proposed Regulation pursues the setting of high standards as regards quality and safety, but also as regards *efficacy* of medicinal products for human use: It ensures, just as regards the aspect of safety, that subjects participating in a clinical trial may receive an efficacious medicine/treatment. It also aims to ensure that the data generated in a clinical trial is reliable and robust not only regarding aspects of quality and safety, but also aspects of *efficacy* of the medicinal product. This aspect of efficacy, however, is not explicitly addressed in Article 168(4)(c) TFEU. Rather, this aspect of public health is addressed through Article 114(3) TFEU (high level of health protection).

Situations like this were dealt with unsatisfactorily until Directive 2001/20/EC came into force. Laws, regulations and administrative acts differed from one Member State to another. These differences forced marketing authorisation holders to adapt their applications for authorisation to place their medicinal product on the market. They also hindered distribution of these products. This had a direct effect on the completion and operation of the internal market.

EU legislation on clinical trials attempts to meet this need. It lays down, at Union level, the rules of procedure to be complied with on aspects such as authorisation and performance of clinical trials, safety reporting, manufacturing and labelling of medicinal products used in a clinical trial.

In regulating clinical trials, the Union exercises its shared competence in accordance with Article 4(2) of the TFEU.

Any changes made to these rules by Member States would conflict with the requirements of the Treaty, as only the Union can amend them.

Having said this, for regulating clinical trials, the Treaty sets limits as regards harmonisation of ethical aspects of authorisation and regulation of clinical trials. Ethical aspects relate, in particular, to the need to obtain ‘informed consent’ from the subject or the legal representative. Irrespective of the risk that a clinical trial may pose to a patient, the mere fact that the treatment is part of an experiment renders it necessary — from an ethical viewpoint — to obtain the informed consent of the subject. Hence, the assessment of aspects related to ‘informed consent’ does not form part of the cooperation amongst Member States, but is assessed by each Member State individually.

There are also several aspects of an intrinsically national nature, in particular:

- Rules for establishing who is a ‘legal representative’ of a subject who cannot give informed consent (for example, because the subject is a child): these rules differ widely across the EU, depending on national tradition and practices;
- Rules on the extent of and prerequisites for liability for damages suffered by a subject: these rules are deeply rooted in national civil law on medical liability. This applies not only to the degree of negligence (e.g. no-fault or objective

liability) but also to the rules on the burden of proof and on calculating the extent of damage.

Consequently, while regulation of clinical trials and, in particular, revision of Directive 2001/20/EC, is compatible with the principle of subsidiarity, there are limits set by the Treaties which have to be considered.

4. BUDGETARY IMPLICATION

The budgetary implications of this proposal are as follows:

- Costs for databases (one-off costs and maintenance);
- Commission staff to manage the functioning of the Regulation;
- Costs for meetings of Member States to ensure that the authorisation procedure set out in this Regulation functions properly;
- Commission staff and other costs to conduct Union controls and Union inspections.

Details of the costs are set out in the legislative financial statement. A thorough discussion on the costs is contained in the impact assessment report.

The costs will be covered with the envelope of the Health for Growth Programme 2014-2020.

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REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

**on clinical trials on medicinal products for human use, and repealing Directive
2001/20/EC**

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168(4)(c) thereof,

Having regard to the proposal from the Commission¹³,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee¹⁴,

Having regard to the opinion of the Committee of the Regions¹⁵,

After consulting the European Data Protection Supervisor¹⁶,

Acting in accordance with the ordinary legislative procedure¹⁷,

Whereas:

- (1) In a clinical trial the safety and rights of subjects should be protected and the data generated should be reliable and robust.
- (2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.
- (3) The existing definition of a clinical trial as contained in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal

¹³ OJ C , , p. .

¹⁴ OJ C , , p. .

¹⁵ OJ C , , p. .

¹⁶ XXX.

¹⁷ OJ C , , p. .

products for human use¹⁸ should be clarified. For that purpose, the concept of clinical trial should be more precisely defined by introducing the broader concept of 'clinical study' of which the clinical trial is a category. That category should be defined on the basis of specific criteria. This approach takes due account of international guidelines, and is in line with the EU legislation governing medicinal products, which builds on the dichotomy of 'clinical trial' and 'non-interventional study'.

- (4) Directive 2001/20/EC aimed to simplify and harmonise the administrative provisions governing clinical trials in the European Union. However, experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a clinical trial in several Member States. Scientific development however, suggests that future clinical trials will target more specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such trials it may be necessary to involve many, or all, Member States. The new procedures for the authorisation of clinical trials should stimulate the inclusion of as many member states as possible. Therefore, in order to simplify submission procedures, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier through a single submission portal to all the Member States concerned.
- (5) Experience with Directive 2001/20/EC has also shown that the aim of simplifying and harmonising the administrative provisions governing clinical trials in the Union cannot be achieved in the legal form of a Directive but can only be achieved with the legal form of a Regulation. Only the legal form of a Regulation ensures that the Member States base their assessment of an application for authorisation of a clinical trial on identical criteria, rather than on diverging national transposition measures. This holds not only for the entire authorisation process, but also for all other issues addressed in this Regulation, such as safety reporting during clinical trials, and the requirements for labelling of the medicinal products used in the context of a clinical trial.
- (6) The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation should not include aspects of an intrinsically national nature, nor ethical aspects of a clinical trial, such as informed consent.
- (7) The procedure should be flexible and efficient, in order to avoid administrative delays for starting a clinical trial.
- (8) The timelines for assessing an application dossier for clinical trials should be sufficiently long to assess the file, while ensuring quick access to new, innovative treatments and ensuring that the Union remains an attractive place for conducting clinical trials. Against this background, Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to. In the event of a public health crisis, Member States should have the possibility to assess and authorise a clinical trial application swiftly. No minimal timelines for approval should therefore be established.

¹⁸ OJ L 121, 1.5.2001, p. 34.

- (9) The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is in particular the case where the investigational medicinal product is covered by a marketing authorisation (i.e. the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure) and where the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those "low-intervention clinical trials" are often of crucial importance to assess standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. They should be subject to less stringent rules, such as shorter deadlines for approval.
- (10) The assessment of the application for a clinical trial should address in particular the anticipated therapeutic and public health benefits ('relevance') and the risk and inconveniences for the subject. Regarding the relevance, numerous aspects should be taken into account, including whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products.
- (11) The authorisation procedure should provide for the possibility to suspend the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. The maximum duration of the suspension should reflect whether the clinical trial is a low-intervention clinical trial or not. Moreover, it should be ensured that, following the end of the suspension, there is always sufficient time for assessing the additional information submitted.
- (12) Some aspects in a clinical trial application relate to issues of an intrinsic national nature or to ethical aspects of a clinical trial. Those issues should not be assessed in cooperation among all Member States concerned.
- (13) The authorisation of a clinical trial should address all aspects in relation to subject protection and data reliability and robustness. The permission to conduct a clinical trial should therefore be contained in one single administrative decision by the Member State concerned.
- (14) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in this assessment. This decision is a matter of internal organisation of each Member State. Member States, when determining the appropriate body or bodies, should ensure the involvement of lay persons and patients. They should also ensure that the necessary expertise is available. In any case, however, and in accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent from the sponsor, the institution of the trial site, and the investigators involved, as well as free of any other undue influence.
- (15) In practice, when submitting an application for authorisation of a clinical trial, sponsors do not always have full certainty about the Member States where a clinical trial is eventually going to be conducted. It should be possible for sponsors to submit an application solely on the basis of the documents assessed jointly by those Member States where the clinical trial might be conducted.

- (16) The sponsor should be allowed to withdraw the application for authorisation of a clinical trial. To ensure the reliable functioning of the assessment procedure, however, an application for authorisation of a clinical trial should be withdrawn only for the entire clinical trial. It should be possible for the sponsor to submit a new application for authorisation of a clinical trial following the withdrawal of an application.
- (17) In practice, in order to reach recruitment targets or for other reasons, sponsors may have an interest to extend the clinical trial to an additional Member States after the initial authorisation of the clinical trial. An authorisation mechanism should be provided to allow for this extension, while avoiding the re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial.
- (18) Clinical trials are usually subject to many modifications after they have been authorised. Those modifications may relate to the conduct, design, methodology, investigational or auxiliary medicinal product, or the investigator or trial site involved. Where those modifications have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial, they should be subject to an authorisation procedure similar to the initial authorisation procedure.
- (19) The content of the application dossier for authorisation of a clinical trial should be harmonised in order to ensure that all Member States have the same information available and to simplify the application process for clinical trials.
- (20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly accessible database.
- (21) It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined to the subject.
- (22) The human dignity and right to the integrity of the person are recognized in the Charter of Fundamental rights of the European Union. In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned. Directive 2001/20/EC contained an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legal representative of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legal representative of incapacitated persons and minors.
- (23) This Regulation should provide for clear rules concerning informed consent in emergency situations. Such situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in certain circumstances, due to the unconsciousness of the patient

and the absence of an immediately available legal representative, it is not possible to obtain informed consent prior to the intervention. The Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions. In addition, the said clinical trial should relate directly to the medical condition which causes the impossibility of the patient to give informed consent. Any previously expressed objection by the patient must be respected, and informed consent from the subject or the legal representative should be sought as soon as possible.

- (24) In accordance with international guidelines, the free and informed consent of the subject should be in writing, save in exceptional situations. It should be based on information which is clear, relevant and understandable to the subject.
- (25) In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of recruitment for the clinical trial and the end of the clinical trial should be notified. In accordance with international standards, the results of the clinical trial should be reported to the competent authorities within one year of the end of the clinical trial.
- (26) In order for the sponsor to assess all potentially relevant safety information, the investigator should report to him all serious adverse events.
- (27) The sponsor should assess the information received from the investigator, and report safety information on serious adverse events which are suspected unexpected serious adverse reactions to the Agency.
- (28) The Agency should forward this information to the Member States for them to assess this information.
- (29) The members of the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) have agreed on a detailed set of guidelines for good clinical practice which are now an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. In such a case, the ICH guidelines on good clinical practice should be used as guidance for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission and that those guidelines are without prejudice to this Regulation.
- (30) The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into account the characteristics of the clinical trial and respect for fundamental rights of subjects. When establishing the extent of monitoring, the characteristics of the clinical trial should be taken into account.
- (31) The individuals involved in conducting the clinical trial, in particular investigators and other healthcare staff, should be sufficiently qualified to perform their tasks in a clinical trial and the facilities where the clinical trial is to be conducted should be suitable for the clinical trial.

- (32) Depending on the circumstances of the clinical trial, it should be possible to trace the investigational and certain auxiliary medicinal products in order to ensure subject safety and data robustness and reliability. For the same reasons, those products should be destroyed where necessary and, depending on the circumstances of the clinical trial, subject to specific storage conditions.
- (33) During a clinical trial, a sponsor may become aware of serious breaches of the rules for the conduct of the clinical trial. This should be reported to the Member States concerned in order for action to be taken by those Member States, where necessary.
- (34) Apart from the reporting of suspected unexpected serious adverse reactions, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner to the Member States concerned.
- (35) Where unexpected events require an urgent modification of a clinical trial, it should be possible for the sponsor and the investigator to take urgent safety measures without awaiting prior authorisation.
- (36) In order to ensure compliance of the conduct of the clinical trial with the protocol, and in order for investigators to be informed about the investigational medicinal products they administer, the sponsor should supply the investigators with an investigator's brochure.
- (37) The information generated in the clinical trial should be recorded, handled and stored adequately for the purpose of ensuring subject rights and safety, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States or the Commission.
- (38) In order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file, containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States and the Commission), should be kept by the sponsor and by the investigator. The clinical trial master file should be archived appropriately to allow for supervision after the clinical trial has ended.
- (39) Medicinal products intended for research and development trials fall outside the scope of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use¹⁹. Such medicinal products include medicinal products used in the context of a clinical trial. They should be covered by specific rules taking account of their peculiarities. In establishing these rules, a distinction should be made between investigational medicinal products (the tested product and its reference products, including placebos) and auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products), such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal

¹⁹ OJ L 311, 28.11.2001, p. 67.

products should not include concomitant medications, i.e. medications unrelated to the clinical trial and not relevant for the design of the clinical trial.

- (40) In order to ensure subject safety and the reliability and robustness of data generated in a clinical trial, and in order to allow for the distribution of investigational and auxiliary medicinal products to clinical trial sites throughout the Union, rules on the manufacturing and importation of both investigational and auxiliary medicinal products should be established. As is already the case for Directive 2001/20/EC, those rules should reflect the existing rules of good manufacturing practices for products covered by Directive 2001/83/EC. In some specific cases, it should be possible to allow deviations from those rules in order to facilitate the conduct of a clinical trial. Therefore, the applicable rules should allow for some flexibility, provided that subject safety, as well as reliability and robustness of the data generated in the clinical trial are not compromised.
- (41) Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial, and in order to allow for the distribution of those products to clinical trial sites throughout the Union. The rules for labelling should be adapted to the risks to subject safety and the reliability and robustness of data generated in a clinical trial. Where the investigational or auxiliary medicinal product have already been placed on the market as an authorised medicinal product in accordance with Directive 2001/83/EC, as a general rule no additional labelling should be required for open-label trials. Moreover, there are specific products, such as radiopharmaceuticals used as diagnostic investigational medicinal product, where the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.
- (42) In order to ensure clear responsibilities the concept of a 'sponsor' of a clinical trial, in line with international guidelines, was introduced with Directive 2001/20/EC. This concept should be upheld.
- (43) In practice, there may be loose, informal networks of researchers or research institutions which run jointly a clinical trial. Those networks should be able to be co-sponsors of a clinical trial. In order not to weaken the concept of responsibility in a clinical trial, where a clinical trial has several sponsors, they should all be subject to the obligations of a sponsor under this Regulation. However, the co-sponsors should be able to split up the responsibilities of the sponsor by contractual agreement.
- (44) The sponsor of a clinical trial may be located in a third country. In order to facilitate supervision and control, a sponsor located in a third country should establish a contact person in the Union to allow for the competent authority of the Member State concerned to communicate with the sponsor. That contact person may be a legal or a natural person.
- (45) Where, in the course of a clinical trial, damage caused to the subject leads to the civil or criminal liability of the investigator or the sponsor, the conditions for liability in such cases, including issues of causality and the level of damages and sanctions, should remain governed by national legislation.

- (46) In clinical trials with non-authorised investigational medicinal products, or where the intervention poses more than an insignificant risk to subject safety, compensation should be ensured for damages successfully claimed in accordance with the applicable laws.
- (47) At present, such damage compensation is provided by way of insurance. This insurance may cover damages to be paid to the subject by the sponsor and investigator in the case of established liability. It may also compensate the subject directly without prior establishment of the liability of the sponsor or investigator. Experience shows that the insurance market is small and costs for insurance coverage are disproportionately high. Moreover, as liability regimes differ widely between Member States, it is difficult and burdensome for the sponsor of a multinational trial to obtain insurance in accordance with those national laws. Therefore, each Member State should establish a national indemnification mechanism which compensates subjects in accordance with the laws of that Member State.
- (48) The Member State concerned should be given the power to early terminate, suspend or modify a clinical trial.
- (49) In order to ensure compliance with this Regulation, Member States should be able to conduct inspections and should have adequate inspection capacities.
- (50) The Commission should be able to control whether Member States correctly supervise compliance with this Regulation. Moreover, the Commission should be able to control whether regulatory systems of third countries ensure compliance with the specific provisions of this Regulation and Directive 2001/83/EC concerning clinical trials conducted in third countries.
- (51) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the Commission should set up and maintain a database, accessed through a portal.
- (52) The database should contain all relevant information as regards the clinical trial. No personal data of data subjects participating in a clinical trial should be recorded in the database. The information in the database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter of Fundamental Rights of the European Union.
- (53) Within a Member State, there may be several bodies involved in the authorisation of clinical trials. In order to allow for effective and efficient cooperation between Member States, each Member State should designate one contact point.
- (54) The authorisation procedure set up in this Regulation is largely controlled by Member States. Nevertheless, the Commission should support the good functioning of this procedure, in accordance with this Regulation.
- (55) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees. However, Member States should not require multiple payments to different bodies assessing, in a given Member State, an application for authorisation of a clinical trial.

- (56) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission to adopt implementing acts in relation to inspections. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers²⁰.
- (57) In order to ensure that information and documentation submitted in an application for authorisation of a clinical trial or a substantial modification allows assessment of the application in view of technical progress and global regulatory requirements, and in order to ensure a high level of subject protection and reliability and robustness of data generated in a clinical trial through a well-functioning safety reporting process and through detailed requirements for manufacturing and labelling of medicinal products used in the context of a clinical trial, the Commission should be empowered to adopt delegated acts in accordance with Article 290 of the Treaty on the Functioning of the European Union to amend the list of documentation and information to be submitted in an application for authorisation of a clinical trial or a substantial modification, to amend technical aspects for safety reporting in the context of a clinical trial, to adopt detailed requirements of good manufacturing practice, and to amend the list of information to appear on the labelling of medicinal products used in the context of a clinical trial. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level. The Commission, when preparing and drawing-up delegated acts, should ensure a simultaneous, timely and appropriate transmission of relevant documents to the European Parliament and Council.
- (58) Article 4(5) of Directive 2001/83/EC provides that national legislation prohibiting or restricting the use of any specific type of human or animal cells should, in principle, not be affected by that Directive and all the Regulations referred to therein. Likewise, this Regulation should not affect national legislation prohibiting or restricting the use of any specific type of human or animal cells. As in Directive 2001/83/EC, Member States should communicate those national provisions to the Commission.
- (59) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data²¹ applies to the processing of personal data carried out in the Member States, under the supervision of the Member States competent authorities, in particular the public independent authorities designated by the Member States and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data²², which applies to the processing of personal data carried out by the Commission and the Agency within the framework of this Regulation, under the supervision of the European Data Protection Supervisor.

²⁰ OJ L 55, 28.2.2011, p. 13.

²¹ OJ L 281, 23.11.1995, p. 31.

²² OJ L 8, 12.1.2001, p. 1.

- (60) Without prejudice to the national systems for the cost and reimbursement of medical treatments, subjects should not have to pay for investigational medicinal products.
- (61) The authorisation procedure set up in this Regulation should apply as soon as possible, in order for sponsors to reap the benefits of a streamlined authorisation procedure. However, in order to allow the setting up at Union level of the extensive IT functionalities required for the authorisation procedure, it is appropriate to provide for a reasonable period to elapse before this Regulation applies.
- (62) Directive 2001/20/EC should be repealed to ensure that only one set of rules applies to the conduct of clinical trials in the Union. In order to facilitate the transition to the rules set out in this Regulation, sponsors should be allowed to start and conduct a clinical trial in accordance with Directive 2001/20/EC during a transitional period.
- (63) This Regulation is in line with the major international guidance documents on clinical trials, such as the most recent (2008) version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki.
- (64) This Regulation is based on the double legal basis of Articles 114 and 168(4)(c) TFEU. It aims at achieving an internal market as regards clinical trials and medicinal products for human use, taking as a base a high level of protection of health. At the same time, this Regulation sets high standards of quality and safety for medicinal products to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. Both objectives are inseparably linked and one is not secondary to another: Regarding Article 114 TFEU, this Regulation harmonises the rules for the conduct of clinical trials in the EU therefore ensuring the functioning of the internal market in view of the conduct of a clinical trial in several Member States, the acceptability throughout the Union of data generated in a clinical trial and submitted in the application for the authorisation of another clinical trial or of the placing on the market of a medicinal product, and the free movement of medicinal products used in the context of a clinical trial. Regarding Article 168(4)(c) TFEU, this Regulation sets high standards of the quality and safety of medicinal products by ensuring that data generated in clinical trials is reliable and robust, thus ensuring that treatments and medicines which are supposed to be an improvement of a treatment of patients build on reliable and robust data. Moreover, this Regulation sets high standards of quality and safety of medicinal products used in the context of a clinical trial, thus ensuring the safety of subjects in a clinical trial.
- (65) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science. This Regulation should be applied by the Member States in accordance with those rights and principles.
- (66) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring the safety and rights of subjects, cannot sufficiently be achieved by the Member States and can, by reason of the scale of the measure, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the

Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

HAVE ADOPTED THIS REGULATION:

Chapter I

General provisions

Article 1 *Scope*

This Regulation shall apply to clinical trials conducted in the Union.

It shall not apply to non-interventional studies.

Article 2 *Definitions*

For the purposes of this Regulation, the definitions of "medicinal product", "radiopharmaceutical", "adverse reaction", "serious adverse reaction", "immediate packaging" and "outer packaging" in Article 1(2), (6), (11), (12), (23) and (24) of Directive 2001/83/EC shall apply.

The following definitions shall also apply:

- (1) 'Clinical study': any investigation in relation to humans intended
 - (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
 - (b) to identify any adverse reactions to one or more medicinal products; or
 - (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;with the objective of ascertaining their safety or efficacy.
- (2) 'Clinical trial': a clinical study which fulfils any of the following conditions:
 - (a) the investigational medicinal products are not authorised;
 - (b) according to the protocol of the clinical study, the investigational medicinal products are not used in accordance with the terms of the marketing authorisation of the Member State concerned;
 - (c) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

- (d) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
 - (e) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
- (3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions:
 - (a) the investigational medicinal products are authorised;
 - (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is a standard treatment in any of the Member States concerned;
 - (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.
- (4) 'Non-interventional study': a clinical study other than a clinical trial;
- (5) 'Investigational medicinal product': a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;
- (6) 'Normal clinical practice': the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;
- (7) 'Advanced therapy investigational medicinal product': an investigational medicinal product which is an advanced therapy medicinal product as defined in Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council²³;
- (8) 'Auxiliary medicinal product': a medicinal product used in the context of a clinical trial, but not as an investigational medicinal product;
- (9) 'Authorised investigational medicinal product': a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or, in any Member State concerned, in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product;
- (10) 'Authorised auxiliary medicinal product': a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or, in any Member State concerned, in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product;
- (11) 'Member State concerned': the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II and III of this Regulation;

²³ OJ L 324, 10.12.2007, p. 121.

- (12) 'Substantial modification': any change to any aspect of the clinical trial which is made after notification of the decision referred to in Articles 8, 14, 19, 20 and 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial;
- (13) 'Sponsor': an individual, company, institution or organisation which takes responsibility for the initiation and management of the clinical trial;
- (14) 'Investigator': an individual responsible for the conduct of a clinical trial at a clinical trial site;
- (15) 'Subject': an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;
- (16) 'Minor': a subject who is, according to the laws of the Member State concerned, under the age of legal competence to give informed consent;
- (17) 'Incapacitated subject': a subject who is, for other reasons than the age of legal competence to give informed consent, legally incapable of giving informed consent according to the laws of the Member State concerned;
- (18) 'Legal representative': a natural or legal person, authority or body which, according to the national law of the Member State concerned, gives informed consent for a subject who is incapacitated or a minor;
- (19) 'Informed consent': a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate;
- (20) 'Protocol': a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial;
- (21) 'Manufacturing': total and partial manufacture, as well as the various processes of dividing up, packaging, labelling (including blinding);
- (22) 'Start of the clinical trial': the first act of recruitment of a potential subject, unless defined differently in the protocol;
- (23) 'End of the clinical trial': the last visit of the last subject, unless defined differently in the protocol;
- (24) 'Temporary halt of the clinical trial': interruption of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it;
- (25) 'Suspension of the clinical trial': interruption of the conduct of a clinical trial by a Member State;
- (26) 'Good clinical practice': a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust;

- (27) ‘Inspection’: the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;
- (28) ‘Adverse event’: any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;
- (29) ‘Serious adverse event’: any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, is life-threatening or results in death;
- (30) ‘Unexpected serious adverse reaction’: a serious adverse reaction the nature, severity or outcome of which is not consistent with the reference safety information.

For the purposes of this Regulation, a subject who falls under the definition of both “minor” and “incapacitated subject” shall be considered as an incapacitated subject.

Article 3
General principle

A clinical trial may be conducted only if

- the rights, safety and well-being of subjects are protected; and
- the data generated in the clinical trial are going to be reliable and robust.

Chapter II
Authorisation procedure for a clinical trial

Article 4
Prior authorisation

A clinical trial shall be subject to authorisation in accordance with this Chapter.

Article 5
Submission of an application

1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 77 (hereinafter 'EU portal').

The sponsor shall propose one of the Member States concerned as reporting Member State.

Where the proposed reporting Member State does not wish to be the reporting Member State, it shall agree with another Member State concerned that the latter will be the reporting Member State. If no Member State concerned accepts to be the reporting Member State, the proposed reporting Member State shall be the reporting Member State.

2. Within six days following submission of the application dossier, the proposed reporting Member State shall notify the sponsor through the EU portal of the following:
 - (a) whether it is the reporting Member State or which other Member State concerned is the reporting Member State;
 - (b) whether the clinical trial falls within the scope of this Regulation;
 - (c) whether the application is complete in accordance with Annex I;
 - (d) whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor.
3. Where the proposed reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the clinical trial applied for shall be considered as falling within the scope of this Regulation, the application shall be considered complete, the clinical trial shall be considered a low-intervention clinical trial if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.
4. Where the proposed reporting Member State finds that the application is not complete, that the clinical trial applied for does not fall within the scope of this Regulation, or that the clinical trial is not a low-intervention clinical trial while this is claimed by the sponsor, it shall inform the sponsor thereof through the EU portal and shall set a maximum of six days for the sponsor to comment or to complete the application through the EU portal.

Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.

Where the proposed reporting Member State has not notified the sponsor according to points (a) to (d) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete, the clinical trial shall be considered as falling within the scope of this Regulation, the clinical trial shall be considered as a low-intervention clinical trial if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.

5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 4.

Article 6
Assessment report – Aspects covered by Part I

1. The reporting Member State shall assess the application with regard to the following aspects:
 - (a) Compliance with Chapter V with respect to the following:
 - (i) The anticipated therapeutic and public health benefits taking account of all of the following:
 - the characteristics of and knowledge about the investigational medicinal products;
 - the relevance of the clinical trial, taking account of the current state of scientific knowledge, and of whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products;
 - the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial and methodology (including sample size and randomisation, comparator and endpoints);
 - (ii) The risks and inconveniences for the subject, taking account of all of the following:
 - the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;
 - the characteristics of the intervention compared to normal clinical practice;
 - the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;
 - the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;
 - (b) Compliance with the requirements concerning the manufacturing and importation of investigational medicinal products and auxiliary medicinal products set out in Chapter IX;
 - (c) Compliance with the labelling requirements set out in Chapter X;
 - (d) The completeness and adequateness of the investigator's brochure.
2. The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.
3. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:

- (a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation;
 - (b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion;
 - (c) the conduct of the trial is not acceptable in view of the requirements set out in this Regulation.
4. The reporting Member State shall submit Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within the following time periods:
- (a) within 10 days from the validation date for low-intervention clinical trials;
 - (b) within 25 days from the validation date for clinical trials other than low-intervention clinical trials;
 - (c) within 30 days from the validation date for any clinical trial with an advanced therapy investigational medicinal product.

For the purposes of this Chapter, the assessment date shall be the date on which the assessment report is submitted to the sponsor and to the other Member States concerned.

5. Until the assessment date, any Member State concerned may communicate to the reporting Member State any considerations relevant to the application. The reporting Member State shall take those considerations duly into account.
6. The reporting Member State, and only the reporting Member State, may, between the validation date and the assessment date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining those additional explanations, the reporting Member State may suspend the time period referred to in paragraph 4 for a maximum of 10 days for low-intervention clinical trials and for a maximum of 20 days for trials other than low-intervention clinical trials.

Where, upon receipt of the additional explanations, the remaining time period for submitting Part I of the assessment report is less than three days in the case of low-intervention clinical trials, and less than five days for other than low-intervention clinical trials, it shall be extended to three and five days respectively.

Where the sponsor does not provide additional explanations within the time period set by the reporting Member State in accordance with the second subparagraph, the application shall be considered as withdrawn.

The request for additional explanations and the additional explanations shall be submitted through the EU portal.

7. The sponsor may at its own initiative change the content of the application only between the validation date and the assessment date and only for duly justified reasons. In this case, the reporting Member State may, depending on the extent of the change to the content of the application, suspend the period referred to in paragraph 4 for a maximum of 60 days.

Article 7

Assessment report – Aspects covered by Part II

1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:
 - (a) compliance with the requirements for informed consent as set out in Chapter V;
 - (b) compliance of the arrangements for rewarding or compensating investigators and subjects with the requirements set out in Chapter V;
 - (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;
 - (d) compliance with Directive 95/46/EC;
 - (e) compliance with Article 46;
 - (f) compliance with Article 47;
 - (g) compliance with Article 72;
 - (h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.

The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.

2. Each Member State concerned shall complete its assessment within ten days from the validation date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.
3. For the purpose of obtaining additional explanations from the sponsor, the Member State concerned may suspend the period referred to in paragraph 2 for a maximum of ten days.

Where, upon receiving the additional explanations, the remaining time period for completing the assessment referred to in paragraph 1 is less than five days, it shall be extended to five days.

Where the sponsor does not provide additional explanations within the time period set by the Member State in accordance with the first subparagraph, the application shall be considered as withdrawn. The withdrawal shall apply only with respect to the Member State concerned.

The request and the additional explanations shall be submitted through the EU portal.

Article 8
Decision on the clinical trial

1. Each Member State concerned shall notify the sponsor through the EU Portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ten days from the assessment date or the last day of the assessment referred to in Article 7, whichever is later.

2. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.

Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

- (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;
- (b) infringement of the national legislation referred to in Article 86.

Where the Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.
4. Where the Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the clinical trial.
5. The Member States concerned shall not request additional explanations from the sponsor after the assessment date.
6. For the purposes of this Chapter, the notification date shall be the date on which the decision referred to in paragraph 1 is notified to the sponsor. Where the sponsor has not been notified in accordance with paragraph 1, the notification date shall be the last day of the time period provided for in paragraph 1.

Article 9
Persons assessing the application

1. Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, the institution of the trial site and the investigators involved, as well as free of any other undue influence.
2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.
3. In the assessment, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account.

Article 10
Specific considerations for vulnerable populations

1. Where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics.
2. Where the subjects are incapacitated, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.
3. In applications for authorisation of clinical trials referred to in Article 32, specific consideration shall be given to the circumstances of the conduct of the clinical trial.

Article 11
Submission and assessment of applications limited to aspects covered by Part I of the assessment report

Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the decision shall be limited to the aspects covered by Part I of the assessment report.

After the notification of the decision on the aspects covered by Part I of the assessment report, the sponsor may apply for an authorisation limited to aspects covered by Part II of the assessment report. In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision with regard to Part II of the assessment report in accordance with Article 8.

Article 12
Withdrawal

The sponsor may withdraw the application at any time until the assessment date. In such a case, the application may only be withdrawn with respect to all Member States concerned.

Article 13
Resubmission

This Chapter is without prejudice to the possibility for the sponsor to submit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be considered as a new application for authorisation of another clinical trial.

Article 14
Subsequent addition of a Member State concerned

1. Where the sponsor wishes to extend an authorised clinical trial to another Member State (hereinafter ‘additional Member State concerned’), the sponsor shall submit an application dossier to that Member State through the EU portal.

The application may be submitted only after the notification date of the initial authorisation decision.

2. The reporting Member State for the application referred to in paragraph 1 shall be the reporting Member State for the initial authorisation procedure.
3. The additional Member State concerned shall notify the sponsor through the EU portal by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused within the following time periods:
 - (a) 25 days from the date of submission of the application referred to in paragraph 1 for low-intervention clinical trials;
 - (b) 35 days from the date of submission of the application referred to in paragraph 1 for clinical trials other than low-intervention clinical trials;
 - (c) 40 days from the date of submission of the application referred to in paragraph 1 for any clinical trial with an advanced therapy investigational medicinal product.
4. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the additional Member State concerned shall be the same as that of the reporting Member State referred to in Article 6(3).

Notwithstanding the first subparagraph, an additional Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

- (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;
- (b) infringement of the national legislation referred to in Article 86.

Where the additional Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.

- 5. Between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State any considerations relevant to the application.
- 6. The reporting Member State, and only the reporting Member State, may, between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, request additional explanations from the sponsor concerning Part I of the assessment report, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining those additional explanations, the reporting Member State may suspend the relevant time period referred to in paragraph 3 for a maximum of 10 days for low-intervention clinical trials and for a maximum of 20 days for trials other than low-intervention clinical trials.

Where, upon receipt of the additional explanations, the remaining time period for notifying the decision referred to in paragraph 4 is less than three days in the case of low-intervention clinical trials, and less than five days for other than low-intervention clinical trials, it shall be extended to three and five days respectively.

Where the sponsor does not provide additional explanations within the time period set by the reporting Member State in accordance with the second subparagraph, the application shall be considered as withdrawn.

The request and the additional explanations shall be submitted through the EU portal.

- 7. The additional Member State concerned shall assess, for its territory, the aspects relating to Part II of the assessment report within ten days of the date of submission of the application referred to in paragraph 1. Within this time period it may request, with justified reasons, additional explanations from the sponsor regarding aspects relating to Part II of the assessment report as far as its territory is concerned.
- 8. For the purpose of obtaining the additional explanations, the additional Member State concerned may suspend the period referred to in paragraph 7 for a maximum of ten days. Where, upon receipt of the additional explanations, the remaining time period for assessing the aspects relating to Part II of the assessment report is less than five days, it shall be extended to five days.

The request for additional explanations and the additional explanations shall be submitted through the EU portal.

9. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the additional Member State concerned shall include in its decision its conclusion on Part II of the assessment report.
10. Where the additional Member State concerned has not notified the sponsor of its decision within the relevant time period referred to in paragraph 3, the conclusion on Part I of the assessment report shall be considered as the decision of the additional Member State concerned on the application for authorisation of the clinical trial.
11. A sponsor shall not submit an application in accordance with this Article where a procedure referred to in Chapter III as regards that clinical trial is pending.

Chapter III

Authorisation procedure for a substantial modification of a clinical trial

Article 15 *General principles*

A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

Article 16 *Submission of application*

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal.

Article 17 *Validation of an application for authorisation of a substantial modification of an aspect covered by Part I of the assessment report*

1. The reporting Member State for the authorisation of a substantial modification shall be the reporting Member State for the initial authorisation procedure.
2. Within four days following submission of the application dossier, the reporting Member State shall notify the sponsor through the EU portal of the following:
 - (a) whether the substantial modification concerns an aspect covered by Part I of the assessment report;
 - (b) whether the application is complete in accordance with Annex II;
 - (c) where the clinical trial is a low-intervention clinical trial, whether it will remain a low-intervention clinical trial after its substantial modification.

3. Where the reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the substantial modification applied for shall be considered as concerning an aspect covered by Part I of the assessment report, the application shall be considered as complete and, where the clinical trial is a low-intervention clinical trial, it shall be considered as remaining a low-intervention clinical trial after its substantial modification.
4. Where the reporting Member State finds that the application does not concern an aspect covered by Part I of the assessment report, that the application is not complete, or that the clinical trial will no longer be a low-intervention clinical trial after the substantial modification, contrary to what the sponsor claims, it shall inform the sponsor thereof through the EU portal and shall set a maximum of six days for the sponsor to comment or to complete the application through the EU portal.

Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.

Where the reporting Member State has not notified the sponsor according to points (a) to (c) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete and, where the clinical trial is a low-intervention clinical trial, that it will remain a low-intervention clinical trial after its substantial modification.

5. For the purposes of Articles 18, 19 and 22, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 4.

Article 18

Assessment of a substantial modification of an aspect covered by Part I of the assessment report

1. The reporting Member State shall assess the application and draw up an assessment report.
2. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:
 - (a) the substantial modification is acceptable in view of the requirements set out in this Regulation;
 - (b) the substantial modification is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion;
 - (c) the substantial modification is not acceptable in view of the requirements set out in this Regulation.

3. The reporting Member State shall submit Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within 15 days from the validation date.

For the purposes of this Article and Articles 19 and 23, the assessment date shall be the date on which the assessment report is submitted to the sponsor and to the other Member States concerned.

4. Until the assessment date, any Member State concerned may communicate to the reporting Member State any considerations relevant to the application. The reporting Member State shall take those considerations duly into account.
5. The reporting Member State, and only the reporting Member State, may, between the validation date and the assessment date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining those additional explanations, the reporting Member State may suspend the period referred to in paragraph 4 for a maximum of 10 days.

Where, upon receipt of the additional explanations, the remaining time period for submitting Part I of the assessment report is less than five days, it shall be extended to five days.

Where the sponsor does not provide additional explanations within the time period determined by the reporting Member State in accordance with the second subparagraph, the application shall be considered as withdrawn.

The request and the additional explanations shall be submitted through the EU portal.

6. The sponsor may at its own initiative change the content of the application only between the validation date and the assessment date and only for duly justified reasons. In this case, the reporting Member State may, depending on the extent of the change to the content of the application, suspend the period referred to in paragraph 3 for up to 60 days.

Article 19

Decision on the substantial modification of an aspect covered by Part I of the assessment report

1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ten days from the assessment date.

2. Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.

Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:

- (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;
- (b) infringement of the national legislation referred to in Article 86.

Where the Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where the Member State concerned has not notified the sponsor of its decision within the time period referred to in paragraph 1, the conclusion of the assessment report shall be considered as the decision in the Member State concerned on the application for authorisation of the substantial modification.

Article 20

Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report

1. Within four days following submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:
 - (a) whether the substantial modification concerns an aspect covered by Part II of the assessment report; and
 - (b) whether the application is complete in accordance with Annex II.
2. Where the Member State concerned has not notified the sponsor within the time period referred to in paragraph 1 the substantial modification applied for shall be considered as concerning an aspect covered by Part II of the assessment report and the application shall be considered as complete.
3. Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of six days for the sponsor to comment or to complete the application through the EU portal.

Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.

Where the Member State concerned has not notified the sponsor according to points (a) and (b) of paragraph 1 within three days following receipt of the comments or of the completed application, the substantial modification shall be considered as

concerning an aspect covered by Part II of the assessment report and the application shall be considered as complete.

4. For the purpose of this Article, the date on which the sponsor is notified in accordance with paragraph 1 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 1 and 3.
5. The Member State concerned shall assess the application and shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ten days from the validation date.

6. During the time period referred to in the second subparagraph of paragraph 5 the Member State concerned may request, with justified reasons, additional explanations from the sponsor regarding the substantial modification as far as its territory is concerned.

For the purpose of obtaining additional explanations, the Member State concerned may suspend the time period referred to in the second subparagraph of paragraph 5 for a maximum of ten days.

Where, upon receipt of the additional explanations, the remaining time period for notifying the decision referred to in the second subparagraph of paragraph 5 is less than five days, it shall be extended to five days.

Where the sponsor does not provide additional explanations within the time period set by the Member State in accordance with the first and second subparagraph, the application shall be considered as withdrawn.

The request and the additional explanations shall be submitted through the EU portal.

7. Where the Member State concerned has not notified the sponsor of its decision within the time periods set out in paragraphs 5 and 6, the substantial modification shall be considered as authorised.

Article 21

Substantial modification of aspects covered by Parts I and II of the assessment report

1. Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for authorisation of that substantial modification shall be validated in accordance with Article 17.
2. The aspects covered by Part I of the assessment report shall be assessed in accordance with Article 18 and the aspects covered by Part II of the assessment report shall be assessed in accordance with Article 22.

Article 22

Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report

1. Each Member State concerned shall assess, for its territory, the aspects of the substantial modification which are covered by Part II of the assessment report within ten days from the validation date.
2. During the time period referred to in paragraph 1 the Member State concerned may request, with justified reasons, additional explanations from the sponsor regarding this substantial modification as far as its territory is concerned.
3. For the purpose of obtaining additional explanations from the sponsor, the Member State concerned may suspend the time period referred to paragraph 1 for a maximum of ten days.

Where, upon receipt of the additional explanations, the remaining time period for the assessment referred to in paragraph 1 is less than five days, it shall be extended to five days.

Where the sponsor does not provide additional explanations within the time period referred to in the first and second subparagraph, the application shall be considered as withdrawn.

The request and the additional explanations shall be submitted through the EU portal.

Article 23

Decision on the substantial modification of aspects covered by Parts I and II of the assessment report

1. Each Member State concerned shall notify the sponsor through the EU Portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ten days from the assessment date or the last day of the assessment referred to in Article 22, whichever is later.

2. Where the conclusion of the reporting Member State is that the substantial modification covered by Part I of the assessment report is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.

Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

- (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;
- (b) infringement of the national legislation referred to in Article 86.

Where the Member State concerned disagrees with the conclusion regarding the substantial modification of aspects covered by Part I of the assessment report on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where, regarding the substantial modification of aspects covered by Part I of the assessment report, the substantial modification is acceptable or acceptable subject to conditions, the Member State concerned shall include in its decision its conclusion on the substantial modification of aspects covered by Part II of the assessment report.
4. Where the Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 1, the conclusion on the substantial modification of aspects covered by Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 24

Persons assessing the application

Article 9 applies to the assessments made under this Chapter

Chapter IV

Application dossier

Article 25

Data submitted in the application dossier

1. The application dossier for the authorisation of a clinical trial shall contain all the documentation and information necessary for the validation and assessment referred to in Chapter II and relating to:
 - (a) the conduct of the trial, including the scientific context and arrangements taken,
 - (b) sponsor, investigators, potential subjects, subjects, and trial sites;
 - (c) the investigational medicinal products and, where necessary, the auxiliary medicinal products, in particular their properties, labelling, manufacturing and control;
 - (d) measures to protect subjects.

The list of documentation and information is set out in Annex I.

2. The application dossier for the authorisation of a substantial modification shall contain all the following documentation and information necessary for the validation and assessment referred to in Chapter III:

- (a) a reference to the clinical trial or clinical trials which are substantially modified;
- (b) a clear description of the substantial modification;
- (c) a presentation of data and additional information in support of the substantial modification, where necessary;
- (d) a clear description of the consequences of the substantial modification as regards subject right and safety and reliability and robustness of the data generated in the clinical trial.

The list of documentation and information is set out in Annex II.

- 3. Non-clinical data submitted in an application dossier shall be based on studies complying with Union legislation on the principles of good laboratory practice, as applicable at the time of performance of those studies, or equivalent standards.
- 4. Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation.
- 5. Where the clinical trial has been conducted outside the Union, it shall comply with principles equivalent to those of this Regulation as regards subject rights and safety and reliability and robustness of data generated in the clinical trial.
- 6. Clinical trial data submitted in an application dossier shall be based on clinical trials which have been registered prior to their start in a public register which is a primary registry of the international clinical trials registry platform of the World Health Organisation.
- 7. Data submitted in an application dossier which do not comply with paragraphs 3 to 6 shall not be considered in the assessment of an application for authorisation of a clinical trial or of a substantial modification.

Article 26

Language requirements

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.

Article 27

Update by way of delegated acts

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annexes I and II with the objective to adapt them to technical progress or to take account of global regulatory developments.

Chapter V

Protection of subjects and informed consent

Article 28 *General rules*

1. A clinical trial may be conducted only where all of the following conditions are met:
 - (a) the anticipated therapeutic and public health benefits justify the foreseeable risks and inconveniences;
 - (b) compliance with point (a) is permanently observed;
 - (c) the subject or, where the subject is not able to give informed consent, his or her legal representative has given informed consent;
 - (d) the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of the right to withdraw from the clinical trial at any time without any resulting detriment;
 - (e) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded.
2. The rights, safety and well-being of the subjects shall prevail over the interests of science and society.
3. Any subject may, without any resulting detriment, withdraw from the clinical trial at any time by revoking his or her informed consent. The withdrawal of consent shall not affect the activities carried out based on consent before its withdrawal.

Article 29 *Informed consent*

1. Informed consent shall be written, dated and signed and given freely by the subject or his or her legal representative after having been duly informed of the nature, significance, implications and risks of the clinical trial. It shall be appropriately documented. Where the subject is unable to write, oral consent in the presence of at least one impartial witness may be given in exceptional cases. The subject or his or her legal representative shall be provided with a copy of the document by which informed consent has been given.
2. Written information given to the subject and/or the legal representative for the purposes of obtaining his or her informed consent shall be kept concise, clear, relevant, and understandable to a lay person. It shall include both medical and legal

information. It shall inform the subject about his or her right to revoke his or her informed consent.

3. The subject shall be provided with a contact point where he or she may obtain further information.

Article 30

Clinical trials on incapacitated subjects

1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
 - (a) the informed consent of the legal representative has been obtained, whereby consent shall represent the subject's presumed will;
 - (b) the incapacitated subject has received adequate information in relation to his or her capacity for understanding regarding the trial, the risks and the benefits;
 - (c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator;
 - (d) no incentives or financial inducements are given except compensation for participation in the clinical trial;
 - (e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
 - (f) such research relates directly to a life-threatening or debilitating medical condition from which the subject suffers;
 - (g) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;
 - (h) there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject outweighing the risks or will produce no risk at all.
2. The subject shall as far as possible take part in the consent procedure.

Article 31

Clinical trials on minors

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

- (a) the informed consent of the legal representative has been obtained, whereby consent shall represent the minor's presumed will;
 - (b) the minor has received all relevant information in a way adapted to his or her age and maturity, from professionals trained or experienced in working with children, regarding the trial, the risks and the benefits;
 - (c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time, is duly taken into consideration by the investigator in accordance with his or her age and maturity;
 - (d) no incentives or financial inducements are given except compensation for participation in the clinical trial;
 - (e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
 - (f) such research either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
 - (g) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;
 - (h) some direct benefit for the group of patients is obtained from the clinical trial.
2. The minor shall take part in the consent procedure in a manner adapted to his or her age and maturity.

Article 32
Clinical trials in emergency situations

1. By way of derogation from points (c) and (d) of Article 28(1), from points (a) and (b) of Article 30(1) and from points (a) and (b) of Article 31(1), informed consent may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given after the start of the clinical trial provided that all of the following conditions are fulfilled:
- (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;
 - (b) no legal representative is available;
 - (c) the subject has not previously expressed objections known to the investigator;

- (d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;
 - (e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.
2. The informed consent referred to in paragraph 1 shall be obtained, and information on the clinical trial shall be given, in accordance with the following requirements:
- (a) regarding incapacitated subjects and minors, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative and the information referred to in paragraph 1 shall be given as soon as possible to the subject;
 - (b) regarding other subjects, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative or the subject, whichever is sooner and the information referred to in paragraph 1 shall be given as soon as possible to the legal representative or the subject, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legal representative, informed consent to continue the trial shall be obtained from the subject as soon as it is capable of giving informed consent.

Chapter VI

Start, end, suspension, temporary halt, and early termination of a clinical trial

Article 33

Notification of the start of the clinical trial and of the end of the recruitment of subjects

1. The sponsor shall notify each Member State concerned of the start of a clinical trial in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the start of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU portal.

That notification shall be made within 15 days from the end of the recruitment of subjects. In case of re-start of recruitment, paragraph 1 shall apply.

Article 34

End of the clinical trial, early termination of the clinical trial

1. The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the end of the clinical trial through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial.

3. Within one year from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial.

However, where, for scientific reasons, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with an explanation.

4. For the purpose of this Regulation, if a suspended or temporarily halted clinical trial is not restarted, the date of the decision of the sponsor not to restart the clinical trial shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial.
5. Without prejudice to paragraph 3, where the clinical trial provides for a primary completion date prior to the end of the trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the primary completion date.

Article 35

Temporary halt or early termination by the sponsor for reasons of subject safety

For the purposes of this Regulation, the temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance and the restart following such temporary halt of a clinical trial shall be considered as a substantial modification of a clinical trial.

Chapter VII

Safety reporting in the context of a clinical trial

Article 36

Electronic database for safety reporting

The European Medicines Agency established by Regulation (EC) No 726/2004 (hereinafter, the "Agency") shall set up and maintain an electronic database for the reporting provided for in Articles 38 and 39.

Article 37

Reporting of adverse events and serious adverse events by the investigator to the sponsor

1. The investigator shall report to the sponsor adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation in accordance with the reporting requirements and within the time periods specified in the protocol.
2. The investigator shall immediately report serious adverse events to the sponsor unless the protocol provides, for certain adverse events, that no reporting is required. The investigator shall record all serious adverse events. Where necessary, the investigator shall send a follow-up report to the sponsor.
3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

Article 38

Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency

1. The sponsor shall report electronically and without delay to the electronic database referred to in Article 36 all relevant information about suspected unexpected serious adverse reactions to investigational medicinal products insofar as the suspected unexpected serious adverse reaction occurred in a clinical trial conducted by the sponsor, or occurred in a clinical trial related to the sponsor.
2. The time period for reporting shall take account of the severity of the reaction. Where necessary to ensure timely reporting, the sponsor may submit an initial incomplete report followed up by a complete report.
3. Where a sponsor, due to a lack of resources, does not have the possibility to report to the electronic database referred to in Article 36, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1.

Article 39

Annual reporting by the sponsor to the Agency

1. Regarding non-authorised investigational medicinal products other than placebo, and authorised investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation, the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.
2. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the last clinical trial conducted by the sponsor with the investigational medicinal product.

Article 40
Assessment by Member States

1. The Agency shall, by electronic means, forward to the relevant Member States the information reported in accordance with Article 38 and 39
2. Member States shall cooperate in assessing the information reported in accordance with Articles 38 and 39.

Article 41
Annual reporting by the sponsor to the marketing authorisation holder

1. Regarding authorised medicinal products which, according to the protocol, are used in accordance with the terms of the marketing authorisation, the sponsor shall inform annually the marketing authorisation holder of all suspected serious adverse reactions.
2. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the clinical trial.

Article 42
Technical aspects

Technical aspects for safety reporting in accordance with Articles 37 to 41 are contained in Annex III. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annex III for any of the following purposes:

- ensuring a high level of protection of subjects;
- improving the information on the safety of medicinal products;
- adapting technical requirements to technical progress;
- setting up or modifying detailed rules on cooperation on the assessment of the information reported in accordance with Articles 38 and 39;
- taking account of global regulatory developments in the field of clinical trials.

Article 43
Reporting with regard to auxiliary medicinal products

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Directive 2001/83/EC.

Chapter VIII

Conduct of the trial, supervision by the sponsor, training and experience, auxiliary medicinal products

Article 44

Compliance with the protocol and good clinical practice

A clinical trial shall be conducted in accordance with the protocol.

Without prejudice to Union legislation and specific guidelines of the Commission the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall take due account of the quality standards set by the detailed international guidelines on good clinical practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The Commission shall make the detailed international guidelines on good clinical practice referred to in the second paragraph publicly available.

Article 45

Monitoring

The sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of all characteristics of the clinical trial, including the following characteristics:

- (a) whether the clinical trial is a low-intervention clinical trial;
- (b) the objective and methodology of the clinical trial;
- (c) the degree of deviation of the intervention from normal clinical practice.

Article 46

Suitability of individuals involved in conducting the clinical trial

The investigator shall be a medical doctor as defined in national law, or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.

Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training and experience to perform their tasks.

Article 47

Suitability of trial sites

The facilities where the clinical trial is to be conducted shall be suitable for the clinical trial.

Article 48

Tracking, storing, destruction and return of medicinal products

1. Investigational medicinal products shall be traceable, stored, destroyed and returned as appropriate and proportionate to ensure subject safety and the reliability and robustness of the data generated in the clinical trial, taking into account whether the investigational medicinal product is authorised, and whether the clinical trial is a low-intervention clinical trial.

The first subparagraph shall also apply to unauthorised auxiliary medicinal products.

2. The relevant information regarding the traceability, storage, destruction and return of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

Article 49

Reporting of serious breaches

1. Where the sponsor is aware, with respect to a clinical trial for which it is a sponsor, of a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach, it shall notify the Member States concerned, through the EU portal, of that breach within seven days of becoming aware of that breach.
2. For the purposes of this Article, a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of the subjects or the reliability and robustness of the data generated in the clinical trial.

Article 50

Other reporting obligations relevant for subject safety

1. The sponsor shall notify the Member States concerned through the EU portal and without undue delay, of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 38.
2. The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning a clinical trial conducted by that sponsor.

Article 51

Urgent safety measures

1. Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.
2. The sponsor shall without delay inform the Member States concerned, through the EU portal, of the event and the measures taken.
3. This Article is without prejudice to Chapters II and VII.

Article 52
Investigator's brochure

1. The sponsor shall provide the investigator with the investigator's brochure.
2. The investigator's brochure shall contain all clinical and non-clinical data on the investigational medicinal products relevant to the clinical trial.
3. The investigator's brochure shall be updated where new safety information becomes available, and at least once per year.

Article 53
Recording, processing, handling and storage of information

1. All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable legislation on personal data protection.
2. Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network.

Article 54
Clinical trial master file

The sponsor and the investigator shall keep a clinical trial master file.

The content of the clinical trial master file shall allow verification of the conduct of a clinical trial, taking account of all characteristics of the clinical trial, including whether the clinical trial is a low-intervention clinical trial.

The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

Article 55
Archiving of the clinical trial master file

Unless other Union legislation requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least five years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article.

The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the time period referred to in the first paragraph.

Any alteration to the content of the clinical trial master file shall be traceable.

Article 56
Auxiliary medicinal products

1. Only authorised auxiliary medicinal products may be used in a clinical trial.
2. Paragraph 1 shall not apply where no authorised auxiliary medicinal product is available in the Union or where the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product. A justification to this effect shall be included in the protocol.

Chapter IX
**Manufacturing and import of investigational medicinal products
and auxiliary medicinal products**

Article 57
Scope

Notwithstanding Article 1, this Chapter shall apply to the manufacture and import of investigational medicinal products and auxiliary medicinal products.

Article 58
Manufacturing and import authorisation

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.
2. In order to obtain the authorisation referred to in paragraph 1, the applicant shall meet the following requirements:
 - (a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation;
 - (b) it shall have permanently and continuously at its disposal the services of a person who fulfils the conditions set out in Article 49 (2) and (3) of Directive 2001/83/EC (hereinafter ‘qualified person’).
3. The applicant shall specify, in the request for authorisation, the types and pharmaceutical forms of the investigational medicinal product manufactured or

imported, the manufacturing or import operations, the manufacturing process where relevant, the site where the investigational medicinal products are to be manufactured, and detailed information concerning the qualified person.

4. Articles 42 to 46(e) of Directive 2001/83/EC shall apply to the manufacturing and importation authorisation referred to in paragraph 1.
5. Paragraph 1 shall not apply to any of the following processes:
 - (a) re-labelling, re-packaging or reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State to carry out such processes, and if the investigational medicinal products are intended to be used exclusively by those institutions;
 - (b) the manufacture or import of radiopharmaceuticals used as diagnostic investigational medicinal products where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in those institutions;
 - (c) the preparation of medicinal products referred to in Article 3(1) and (2) of Directive 2001/83/EC.
6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.

Article 59

Responsibilities of the qualified person

1. The qualified person shall ensure that each batch of investigational medicinal products manufactured in or imported into the Union complies with the requirements set out in Article 60 and shall certify that those requirements are fulfilled.
2. The certification referred to in paragraph 1 shall be made available by the sponsor at the request of the Member State concerned.

Article 60

Manufacturing and import

1. Investigational medicinal products shall be manufactured in applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard subject safety and the reliability and robustness of clinical data generated in the clinical trial (hereinafter 'good manufacturing practice'). The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to specify the detailed requirements of good manufacturing practice for ensuring the quality of

investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments

2. Paragraph 1 shall not apply to the processes referred to in Article 58(5).
3. Investigational medicinal products imported into the Union shall be manufactured by applying quality standards at least equivalent to those laid down on the basis of this Regulation.

Article 61

Modification of authorised investigational medicinal products

Articles 58, 59 and 60 shall apply to authorised investigational medicinal products only as regards any modification of such products not covered by a marketing authorisation.

Article 62

Manufacturing of auxiliary medicinal products

Where the auxiliary medicinal product is not authorised, and where an authorised auxiliary medicinal product is modified while this modification is not covered by a marketing authorisation, it shall be manufactured by applying the necessary standards to ensure appropriate quality.

Chapter X Labelling

Article 63

Unauthorised investigational and unauthorised auxiliary medicinal products

1. The following information shall appear on the outer packaging and on the immediate packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products:
 - (a) Information to identify contact persons or persons involved in the clinical trial;
 - (b) Information to identify the clinical trial;
 - (c) Information to identify the medicinal product;
 - (d) Information related to the use of the medicinal product.
2. The information to appear on the outer packaging and immediate packaging shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics.

A list of information appearing on the outer packaging and immediate packaging is set out in Annex IV.

Article 64

Authorised investigational and authorised auxiliary medicinal products

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall be labelled
 - (a) in accordance with Article 63(1); or
 - (b) in accordance with Title V of Directive 2001/83/EC.
2. Notwithstanding paragraph 1(b), where the specific circumstances of a clinical trial so require in order to ensure subject safety or the reliability and robustness of data generated in a clinical trial, additional particulars relating to the identification of the trial and of the contact person shall appear on the outer packaging and the immediate packaging of authorised investigational medicinal products. A list of these additional particulars appearing on the outer packaging and immediate packaging is set out in Annex IV.

Article 65

Radiopharmaceutical used as investigational medicinal product for a medical diagnosis

Articles 63 and 64 shall not apply to radiopharmaceuticals used as investigational medicinal product for a medical diagnosis.

The products referred to in the first paragraph shall be labelled appropriately in order to ensure subject safety and the reliability and robustness of data generated in the clinical trial.

Article 66

Language

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

Article 67

Delegated act

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annex IV to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress.

Chapter XI

Sponsor and investigator

Article 68 *Sponsor*

A clinical trial may have one or several sponsors.

Any sponsor may delegate any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor.

The investigator and the sponsor may be the same person.

Article 69 *Co-sponsorship*

1. Where a clinical trial has more than one sponsor, all sponsors shall be subject to the responsibilities of a sponsor under this Regulation, unless the sponsors decide otherwise in a contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.
2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one sponsor responsible for each of the following:
 - (a) compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;
 - (b) providing responses to all questions from subjects, investigators or any Member State concerned regarding the clinical trial;
 - (c) implementing measures taken in accordance with Article 74.

Article 70 *Contact person of the sponsor in the Union*

Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a contact person is established in the Union. That contact person shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that contact person shall be considered as communication to the sponsor.

Article 71 *Liability*

This Chapter shall not affect the civil and criminal liability of the sponsor, investigator, or persons to whom the sponsor has delegated tasks.

Chapter XII

Damage compensation, insurance and national indemnification mechanism

Article 72 *Damage compensation*

For clinical trials other than low-intervention clinical trials, the sponsor shall ensure that compensation in accordance with the applicable laws on liability of the sponsor and the investigator is provided for any damage suffered by the subject. This damage compensation shall be provided independently of the financial capacity of the sponsor and the investigator.

Article 73 *National indemnification mechanism*

1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.
2. The sponsor shall be deemed to comply with Article 72 where it makes use of the national indemnification mechanism in the Member State concerned.
3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.

For all other clinical trials, the use of the national indemnification mechanism may be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.

Chapter XIII

Supervision by Member States, Union inspections and controls

Article 74 *Corrective measures to be taken by Member States*

1. Where a Member State concerned has objective grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures:
 - (a) it may terminate early the clinical trial;
 - (b) it may suspend the clinical trial;
 - (c) it may modify any aspect of the clinical trial.

2. The measures referred to in paragraph 1 shall be communicated to all Member States concerned through the EU portal.

Article 75
Member State inspections

1. Member States shall appoint inspectors to supervise compliance with this Regulation. They shall ensure that those inspectors are adequately qualified and trained.
2. Inspections shall be conducted under the responsibility of the Member State where the inspection takes place.
3. Where a Member State concerned intends to carry out an inspection with regard to one or several clinical trials which are conducted in more than one Member State concerned, it shall notify its intention to the other Member States concerned, the Commission and the Agency, through the EU portal, and shall inform them of its findings after the inspection.
4. The Agency shall coordinate cooperation on inspections between Member States, inspections conducted by Member States in third countries, and inspections conducted in the framework of a marketing authorisation application under Regulation (EC) No 726/2004.
5. Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal to the EU database.

When making the inspection report available to the sponsor, the Member State referred to in the first subparagraph shall ensure that confidentiality is protected.

6. The Commission shall specify the modalities for the inspection procedures by the way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 84(2).

Article 76
Union controls and Union inspections

1. The Commission may conduct controls in order to verify
 - (a) whether Member States correctly supervise compliance with this Regulation;
 - (b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of Annex I to Directive 2001/83/EC is complied with;
 - (c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(3) of this Regulation is complied with.
2. The Commission may conduct inspections where it considers necessary.

Chapter XIV IT Infrastructure

Article 77 EU portal

The Commission shall set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation.

Data and information submitted through the EU portal shall be stored in the EU database referred to in Article 78.

Article 78 EU database

1. The Commission shall set up and maintain a database at Union level (hereinafter, the 'EU database'). The Commission shall be considered controller of the database.

The EU database shall contain the data and information submitted in accordance with this Regulation.

2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification.
3. The EU database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:
 - protecting personal data in accordance with Regulation (EC) No 45/2001;
 - protecting commercially confidential information;
 - ensuring effective supervision of the conduct of a clinical trial by Member States.
4. The EU database shall contain personal data only insofar as this is necessary for the purposes of paragraph 2.
5. No personal data of subjects shall be publicly accessible.
6. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States.

7. The Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected and erased. Within their respective responsibilities, the Commission and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections and deletions shall be carried out as soon as possible, but no later than within 60 days after a request is made by a data subject.

Chapter XV

Cooperation between Member States

Article 79

National contact points

1. Each Member State shall designate one national contact point in order to facilitate the functioning of the procedures set out in Chapters II and III.
2. Each Member State shall communicate the contact point to the Commission. The Commission shall publish a list of the contact points.

Article 80

Support by the Commission

The Commission shall support the functioning of the cooperation of the Member States in the framework of the authorisation procedures referred to in Chapters II and III of this Regulation and the functioning of the cooperation referred to in Article 40(2).

Article 81

Clinical Trials Coordination and Advisory Group

1. A Clinical Trials Coordination and Advisory Group (CTAG), composed of the national contact points referred to in Article 79 is hereby established.
2. The CTAG shall have the following tasks:
 - (a) support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation;
 - (b) assist the Commission in providing for the support referred to in Article 80;
3. The CTAG shall be chaired by a representative of the Commission.
4. The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State.

5. The secretariat shall be provided by the Commission

Chapter XVI

Fees

Article 82

General principle

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles.

Article 83

One fee per activity per Member State

A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.

Chapter XVII

Implementing acts and Delegated acts

Article 84

Committee

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Directive 2001/83/EC. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.
2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

Where the opinion of the committee is to be obtained by written procedure, that procedure shall be terminated without result when, within the time-limit for delivery of the opinion, the chair of the committee so decided or a simple majority of committee members so request.

Article 85

Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.
2. The delegation of power referred to in Articles 27, 42, 60 and 67 shall be conferred on the Commission for an indeterminate period of time from the date of entry into force of this Regulation.

3. The delegation of power referred to in Articles 27, 42, 60 and 67 may be revoked at any time by the European Parliament or by the Council. A decision of revocation shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the Official Journal of the European Union or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.
4. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.
5. A delegated act adopted pursuant to Articles 27, 42, 60 and 67 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of 2 months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by 2 months at the initiative of the European Parliament or the Council.

Chapter XVIII

Miscellaneous provisions

Article 86

Medicinal products containing, consisting of or derived from cells

This Regulation shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, on grounds not dealt with in this Regulation. The Member States shall communicate the national legislation concerned to the Commission.

Article 87

Relation with other legislation

This Regulation shall be without prejudice to, Council Directive 97/43/Euratom²⁴, Council Directive 96/29/Euratom²⁵, Directive 2001/18/EC of the European Parliament and of the Council²⁶, and Directive 2009/41/EC of the European Parliament and of the Council.²⁷

²⁴ OJ L 180, 9.7.1997, p. 22.

²⁵ OJ L 159, 29.6.1996, p. 1.

²⁶ OJ L 106, 17.4.2001, p. 1.

²⁷ OJ L 125, 21.5.2009, p. 75.

Article 88
Investigational medicinal products free of charge for the subject

Without prejudice to the Member States' competence for the definition of their health policy and for the organisation and delivery of health services and medical care, the costs for investigational medicinal products shall not be borne by the subject.

Article 89
Data Protection

1. Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation.
2. Regulation (EC) No 45/2001 shall apply to the processing of personal data carried out by the Commission and the European Medicines Agency pursuant to this Regulation.

Article 90
Civil and criminal liability

This Regulation is without prejudice to national and Union rules on the civil and criminal liability of the sponsor or the investigator.

Chapter XIX **Final provisions**

Article 91
Repeal

1. Directive 2001/20/EC is repealed as of [*please set a specific date - two years after publication of this Regulation*].
2. By way of derogation from the paragraph 1, where the request for authorisation of a clinical trial has been submitted before the date provided for in Article 92(2) [application date] pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until [*please set a specific date – five years after publication of this Regulation*].
3. References to Directive 2001/20/EC shall be construed as references to this Regulation and shall be read in accordance with the correlation table laid down in Annex V.

Article 92
Transitional provision

By way of derogation from Article 91(1), where the request for authorisation of a clinical trial is submitted between [*please set a specific date - two years from the publication of this*

Regulation] and [*please set a specific date - three years after publication*] that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until [*please set a specific date – five years after publication of this Regulation*].

Article 93
Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

It shall apply as from [*please set a specific date - two years after its publication*].

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

For the European Parliament
The President

For the Council
The President

ANNEX I
Application dossier for initial application

1. INTRODUCTION AND GENERAL PRINCIPLES

1. The sponsor shall, where appropriate, refer to previous applications. If these applications have been submitted by another sponsor, a written agreement from that sponsor shall be submitted.
2. The application shall be signed by the sponsor. This signature confirms that the sponsor is satisfied that:
 - the information provided is complete;
 - the attached documents contain an accurate account of the information available;
 - the clinical trial will be conducted in accordance with the protocol.
3. The application dossier for an application referred to in Article 11 shall be limited to sections 2 to 10 of this Annex.
4. Without prejudice to Article 26, the application dossier for an application referred to in Article 14 shall be limited to sections 11 to 17 of this Annex.

2. COVER LETTER

5. The cover letter shall draw attention to peculiarities of the trial.
6. However, in the cover letter it is not necessary to reproduce information already contained in the EU application form, with the following exceptions:
 - specific features of the trial population, such as subjects not able to give informed consent or minors;
 - whether the trial involves the first administration of a new active substance to humans;
 - whether scientific advice relating to the trial or investigational medicinal product has been given by the Agency, the national competent authority of a Member State or third country; and
 - whether the 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 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use²⁸ (if the Agency has already

²⁸ OJ L 378, 27.11.2006, p. 1.

issued a decision on the PIP, the cover letter contains the link to the decision of the Agency on its website);

- whether investigational medicinal products or auxiliary medicinal products are a narcotic and psychotropic;
- whether the sponsor has obtained an orphan designation for the investigational medicinal product or the disease.

7. The cover letter shall indicate where the relevant information is contained in the application dossier.

8. The cover letter shall indicate where in the application dossier the reference safety information is contained for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction.

9. In the case of a resubmission, the cover letter shall highlight the changes as compared to the previous submission.

3. EU APPLICATION FORM

10. The EU application form, duly filled in.

4. PROTOCOL

11. The protocol shall describe the objective, design, methodology, statistical considerations and organisation of a trial.

12. The protocol shall be identified by the title, the sponsor's protocol code number specific for all versions of it (if available), the date and number of the version, to be updated when it is amended, and a short title or name assigned to it.

13. In particular, the protocol shall include:

- a clear and unambiguous definition of the end of the clinical trial in question (in most cases this will be the date of the last visit of the last subject; any exceptions to this are justified in the protocol);
- a discussion of the relevance of the clinical trial and its design to allow assessment in accordance with Article 6;
- an evaluation of the anticipated benefits and risks to allow assessment in accordance with Article 6;
- inclusion and exclusion criteria;
- a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;
- if elderly persons or women are excluded from the clinical trial, an explanation and justification for these exclusion criteria;

- a detailed description of the recruitment and informed-consent procedure, especially when subjects are incapable of giving informed consent;
 - a summary of monitoring arrangements;
 - a description of the publication policy;
 - a description of the arrangements for taking care of the subjects after their participation in the trial has ended, where such additional care is necessary because of the subjects' participation in the trial and where it differs from that normally expected for the medical condition in question;
 - a description of the arrangements, if any, for tracing, storing, destroying and returning the investigational medicinal product and auxiliary medicinal product in accordance with Article 48;
 - 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;
 - a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects concerned in clinical trials;
 - a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects;
 - duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year;
 - a justification for the use of non-authorised auxiliary medicinal products.
14. If a clinical trial is conducted with an active substance available in the European 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.
15. With regard to the notification of adverse events, the protocol shall identify
- adverse events or laboratory anomalies that are critical to safety evaluations and are to be reported to the sponsor; and
 - serious adverse events which do not require reporting by the investigator.
16. Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.
17. The protocol shall be accompanied by a synopsis of the protocol.

5. INVESTIGATOR'S BROCHURE (IB)

18. The purpose of the IB is to provide the investigators and others involved in the 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.
19. 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 trial and be presented in the form of summaries.
20. If the investigational medicinal product is authorised, and is used according to 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.
21. For a multinational trial where the medicinal product to be used in each Member State is the one authorised at national level, and the SmPC varies among Member States, the sponsor shall choose one SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.
22. If the IB is not a SmPC, it shall contain a clearly identifiable section determining what adverse reactions are to be considered as expected adverse reactions, including information on the frequency and nature of the adverse reactions ('reference safety information').

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

23. As regards documentation relating to GMP compliance, the following shall apply.
24. In the following cases, no documentation needs to be submitted:
 - the IMP is authorised, is not modified, and is manufactured in the EU; or
 - the IMP is not manufactured in the EU, but is authorised and is not modified.
25. If the IMP 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 EU, the following documentation shall be submitted:

- a copy of the importation authorisation as referred to in Article 58; and
 - certification by the qualified person in the EU that the manufacturing complies with GMP at least equivalent to the GMP in the EU, unless there are specific arrangements provided for in mutual recognition agreements between the EU and third countries.
26. In all other cases, a copy of the manufacturing/importing authorisation as referred to in Article 58 shall be submitted.
27. For IMPs the manufacturing or importation of which is not subject to an authorisation in accordance with Article 58, documentation to demonstrate compliance with the requirements referred to in Article 58(6) shall be submitted.

7. IMP DOSSIER (IMPD)

28. The IMPD shall give information on the quality of any IMP, the manufacture and control of the IMP, and data from non-clinical studies and from its clinical use.

7.1.1. Data relating to the IMP

7.1.1.1. Introduction

29. 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 7.1.2.
30. The IMPD shall be prefaced with a detailed table of contents and a glossary of terms.
31. 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.

7.1.1.2. Quality data

32. Quality data shall be submitted in a logical structure.

7.1.1.3. Non-clinical pharmacology and toxicology data

33. The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any IMP used in the clinical trial. 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.
34. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as the headings of the current version of Module 4 of the *Common Technical Document*, or the eCTD format.

35. 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.
36. The IMPD shall contain a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3).
37. 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.

7.1.1.4. Previous clinical trial and human experience data

38. Clinical trial and human experience data shall be submitted in a logical structure, such as the headings of the current version of Module 5 of the *Common Technical Document*, or of the eCTD format.
39. This section shall provide summaries of all available data from previous clinical trials and human experience with the IMPs.
40. It shall contain a statement of the GCP compliance of the clinical trials referred to, as well as a reference to the public entry referred to in Article 25(4) to (6).

7.1.1.5. Overall risk and benefit assessment

41. 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 proposed 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.
42. Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the IMP, 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.

7.1.2. *Simplified IMPD by referring to other documentation*

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

7.1.2.1. Possibility to refer to the IB

44. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the 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 IMP and the safety of its use in the proposed 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.

7.1.2.2. Possibility to refer to the SmPC

45. The applicant may submit the current version of the SmPC as the IMPD if the IMP is authorised. The exact requirements are detailed in Table 1.

Table 1: Content of simplified IMPD

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The IMP is authorised or has a marketing authorisation in an ICH country and is used in the trial: - within the conditions of the SmPC - outside the conditions of the SmPC - after modification (e.g. blinding)	SmPC		
	SmPC	If appropriate	If appropriate
	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the IMP is authorised or has a marketing authorisation in an ICH country and the IMP is supplied by the marketing authorisation holder	SmPC+P+A	Yes	Yes
The IMP 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 - is supplied by another manufacturer	Reference to previous submission		
	SmPC+P+A	Yes	Yes
	SmPC+S+P+A	Yes	Yes
The IMP was subject to a previous clinical trial application and authorised in the Member State concerned and <u>has not been modified</u> and - no new data are available since last amendment to the CTA - new data are available since last amendment to the CTA - is used under different conditions	Reference to previous submission		
	New data	New data	New data
	If appropriate	If appropriate	If appropriate

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

46. If the IMP is defined in the protocol in terms of active substance or ATC code (see above, section 4), 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 IMP in the clinical trial.

7.1.3. IMPD in cases of placebo

47. If the IMP 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, is manufactured by the same manufacturer, and is not sterile.

8. AUXILIARY MEDICINAL PRODUCT DOSSIER

48. Without prejudice to Article 62, the documentation requirements set out in sections 6 and 7 shall also apply also for auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information is submitted.

9. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

49. 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.
50. 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 2).

10. CONTENT OF THE LABELLING OF THE IMPs

11. RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

51. Unless described in the protocol, a separate document shall describe in detail the procedures for enrolment of subjects.
52. 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 the planned arrangements for information or advice to the respondents found not to be suitable for inclusion in the trial.

12. SUBJECT INFORMATION AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)

53. All information to the subjects (or, where applicable, the parents or legal representative) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent.
54. Description of procedures relating to informed consent in specific circumstances to be submitted:
- in trials with minors or incapacitated subjects, the procedures to obtain informed consent from the parent(s) or legal representative, and the involvement of the minor or incapacitated subject shall be described;

- if a procedure with witnessed consent is to be used, relevant information on the reason for using a witness, on the selection of the witness and on the procedure for obtaining informed consent shall be provided.
 - in the case of clinical trials as referred to in Article 32, the procedure for obtaining the informed consent of the legal representative and the subject to continue the clinical trial shall be described.
 - in the case of clinical trials in emergency situations, description of the procedures followed to identify the urgency situation and to document it.
55. In these cases, the information given to the subject and to the parents or legal representative shall be provided.

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

56. A list of the planned clinical trial sites, the name and position of the investigators responsible for a team of investigators conducting a clinical trial at a clinical trial site ('principal investigator') and the number of subjects at the sites shall be submitted.
57. Description of the qualification of the principal investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of GCP or experience obtained from work with clinical trials and patient care shall be described.
58. Any conditions, such as economic interests, that might be suspected to influence the impartiality of the principal investigators shall be presented.

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

59. A written statement on the suitability of the trial sites by the head of the clinic/institution at the trial site or by some other responsible person, according to the system in the Member State shall be submitted.

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

16. FINANCIAL ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

60. Information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.
61. Description of any agreement between the sponsor and the site shall be submitted.

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

ANNEX II
Application dossier for substantial modification

1. INTRODUCTION AND GENERAL PRINCIPLES

1. Where a substantial modification concerns more than one clinical trial of the same sponsor and the same IMP, the sponsor may make a single request for authorisation. The cover letter and the notification contain a list of all clinical trials affected with their official identification numbers and respective modification code numbers.
2. The application shall be signed by the sponsor. This signature confirms that the sponsor is satisfied that:
 - the information provided is complete;
 - the attached documents contain an accurate account of the information available;
 - the clinical trial will be conducted in accordance with the amended documentation.

2. COVER LETTER

3. A cover letter with the following information
 - in its subject line the EU trial number and the sponsor protocol number (if available) with the title of the trial and the sponsor's modification code number allowing unique identification of the substantial modification, whereby care is taken to use the code number consistently;
 - identification of the applicant;
 - identification of the modification (sponsor's substantial modification code number and date), whereby one modification could refer to several changes in the protocol or scientific supporting documents;
 - a highlighted indication of any special issues relating to the modification and an indication as to where the relevant information or text is in the original application dossier;
 - identification of any information not contained in the modification application form that might impact on the risk to subjects;
 - where applicable, a list of all affected clinical trials with official identification numbers and respective modification code numbers (see above).

3. MODIFICATION APPLICATION FORM

4. DESCRIPTION OF THE MODIFICATION

4. The modification shall be described as follows:

- an extract from the amended documents showing previous and new wording in track changes, as well as an extract showing only the new wording;
- notwithstanding the previous point, 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).

5. The new version shall be identified by the date and an updated version number.

5. SUPPORTING INFORMATION

6. Additional supporting information shall include where applicable:

- summaries of data;
- an updated overall risk/benefit assessment;
- possible consequences for subjects already included in the trial;
- possible consequences for the evaluation of the results.

6. UPDATE OF EU APPLICATION FORM

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

ANNEX III
Safety reporting

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

1. An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product.
2. The investigator shall report the serious adverse events referred to in Article 37(2) immediately following knowledge of the serious adverse event. If necessary, a follow-up report shall be sent to allow the sponsor to determine whether the serious adverse event requires reassessment of the benefit-risk balance of the clinical trial.
3. The investigator shall be responsible for reporting to the sponsor all serious adverse events in relation to subjects treated by him or her in the clinical trial. The investigator does not need to actively monitor subjects for adverse events once the trial has ended with regard to the subjects treated by him, unless otherwise provided for in the protocol.
4. Serious adverse events occurring to a subject after the end of the trial with regard to the subjects treated by him shall be reported to the sponsor if the investigator becomes aware of them.

2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARs) BY THE SPONSOR TO THE AGENCY

2.1. Serious event, ‘reaction’

5. A medical event which requires an intervention to prevent one of the characteristics/consequences referred to in point 29 of the second paragraph of Article 2 is a serious adverse event.
6. The definition of adverse reaction covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.
8. In the absence of information on causality from the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this aspect. 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'

9. Regarding unexpectedness, reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction shall constitute unexpected events.
10. The expectedness of an adverse reaction shall be determined by the sponsor in the reference safety information ('RSI'). This is done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.
11. The RSI is contained in the Summary of product characteristics ('SmPC') or the investigator's brochure (IB). The covering letter which is submitted with the application dossier shall refer to the RSI. If the IMP is authorised in several Member States concerned with different SmPCs, the sponsor shall select the most appropriate SmPC, with reference to subject safety, as RSI.
12. The RSI may change during the conduct of a clinical trial. For the purpose of reporting of suspected unexpected serious adverse reactions (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.
13. If information on expectedness has been made available by the reporting investigator, this shall be taken into consideration by the sponsor.

2.3. Detailed scope of SUSARs to be reported

14. The sponsor of a clinical trial performed in at least one Member State shall report the following SUSARs:
 - all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or third country concerned; and
 - all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country, if that clinical trial is
 - sponsored by the same sponsor; or
 - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor. Provision of the IMP or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.
15. SUSARs identified after the end of the trial shall be reported as well.

2.4. Time limits for reporting fatal or life-threatening SUSARs

16. For fatal and life-threatening SUSARs the sponsor shall report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case.
17. If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor shall submit a completed report based on the initial information within an additional eight days.
18. 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.
19. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information shall be reported as a follow-up report within 15 days.

2.5. Time limits for reporting non-fatal or non-life-threatening SUSARs

20. SUSARs which are not fatal and not life-threatening shall be reported within 15 days.
21. If a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, the non-fatal or non-life-threatening SUSAR shall be reported as soon as possible, but within 15 days. The fatal or life-threatening SUSAR follow-up report shall be made as soon as possible, but within a maximum of seven days after first knowledge of the reaction being fatal or life-threatening. Regarding the follow-up report, see section 2.4.
22. 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, while the initial report has not yet been submitted, a combined report shall be created.

2.6. Unblinding treatment allocation

23. Only SUSARs on which the treatment allocation of the subject is unblinded shall be reported by the sponsor.
24. The investigator shall only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the subject.
25. As regards the sponsor, when an event may be a SUSAR the blind shall be broken by the sponsor only for that specific subject. The blind shall be maintained for persons responsible for the ongoing conduct of the trial (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the trial, such as biometrics personnel. Unblinded information shall only be accessible to those who need to be involved in the safety reporting to the Agency, Data Safety Monitoring Boards ('DSMB'), or persons performing ongoing safety evaluations during the trial.
26. However, for trials in high morbidity or high mortality disease, where efficacy endpoints 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 would be treated as disease-related and not subject to systematic unblinding and expedited reporting.

27. In all cases, following unblinding, if the event turns out to be a SUSAR (for example as regards expectedness), the reporting rules for SUSARs shall apply.

3. ANNUAL SAFETY REPORTING BY THE SPONSOR

28. The report shall contain, in an appendix, the RSI in effect at the start of the reporting period.
29. The RSI in effect at the start of the reporting period shall serve as RSI during the reporting period.
30. 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
IMP and AMP labelling

1. UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

1.1. 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) pharmaceutical form, route of administration, quantity of dosage units, and, in the case of open label trials, the name/identifier and strength/potency;
 - (c) the batch or code number identifying the contents and packaging operation;
 - (d) a 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;
 - (f) the name of the investigator (if not included in (a) or (d));
 - (g) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);
 - (h) ‘For clinical trial use only’ or similar wording;
 - (i) the storage conditions;
 - (j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity;
 - (k) ‘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 need not appear on the label where 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.

1.2. Limited labelling of immediate packaging

1.2.1. Immediate and outer packaging provided together

4. When the product is provided to the subject or the person administering the medication in an immediate package and outer packaging intended to remain together, and the outer packaging carries the particulars listed in section 1.1., 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 open label trials, the name/identifier and strength/potency;
 - (c) batch and/or code number identifying the contents and packaging operation;
 - (d) a 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.

1.2.2. 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 1.1. cannot be displayed, the outer packaging is provided bearing 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 open label trials, the name/identifier and strength/potency;
 - (c) batch or code number identifying the contents and packaging operation;
 - (d) a 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.

2. 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) trial reference code allowing identification of the trial site, investigator and subject.

3. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

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

- a) name of the main contact;
- b) trial reference code allowing identification of the trial site, investigator and subject.

4. REPLACING OF INFORMATION

8. Any of the particulars listed in sections 1, 2, and 3 may be omitted and replaced by other means (e.g. use of a centralised electronic randomisation system, use of a centralised information system) provided that subject safety and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

ANNEX V
Correlation table

Directive 2001/20/EC	This Regulation
Article 1(1)	Articles 1, 2, 1 st paragraph, 2 nd paragraph (1), (2), (4)
Article 1(2)	Article 2, 2 nd paragraph (26)
Article 1(3), 1st subparagraph	-
Article 1(3), 2nd subparagraph	Article 44, 3 rd subparagraph
Article 1(4)	Article 44, 2 nd subparagraph
Article 2	Article 2
Article 3(1)	-
Article 3(2)	Article 4, 28, 29(1), 72
Article 3(3)	-
Article 3(4)	Article 29(3)
Article 4	Articles 28, 31, 10(1)
Article 5	Articles 28, 30, 10(2)
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 51
Article 10(c)	Articles 34, 35
Article 11	Article 78
Article 12	Article 74
Article 13(1)	Article 58(1) to (4)
Article 13(2)	Article 58 (2)

Article 13(3), 1 st subparagraph	Article 59(1), 60(1), (3)
Article 13(3), 2 nd subparagraph	Article 60(1)
Article 13(3), 3 rd subparagraph	-
Article 13(4)	Article 59(2)
Article 13(5)	-
Article 14	Article 63-67
Article 15	Article 75
Article 16	Article 37
Article 17(1)(a) to (c)	Article 38
Article 17(1)(d)	-
Article 17(2)	Article 39
Article 17(3)(a)	-
Article 17(3)(b)	Article 40(1)
Article 18	-
Article 19, 1 st paragraph, 1 st sentence	Article 71
Article 19, 1 st paragraph, 2 nd sentence	Article 70
Article 19, 2 nd paragraph	Article 88
Article 19, 3 rd paragraph	-
Article 20	-
Article 21	Article 84
Article 22	-
Article 23	-
Article 24	-

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

- 1.1. Title of the proposal/initiative
- 1.2. Policy area(s) concerned in the ABM/ABB structure
- 1.3. Nature of the proposal/initiative
- 1.4. Objective(s)
- 1.5. Grounds for the proposal/initiative
- 1.6. Duration and financial impact
- 1.7. Management method(s) envisaged

2. MANAGEMENT MEASURES

- 2.1. Monitoring and reporting rules
- 2.2. Management and control system
- 2.3. Measures to prevent fraud and irregularities

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

- 3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected
- 3.2. Estimated impact on expenditure
 - 3.2.1. *Summary of estimated impact on expenditure*
 - 3.2.2. *Estimated impact on operational appropriations*
 - 3.2.3. *Estimated impact on appropriations of an administrative nature*
 - 3.2.4. *Compatibility with the current multiannual financial framework*
 - 3.2.5. *Third-party participation in financing*
- 3.3. Estimated impact on revenue

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

1.1. Title of the proposal/initiative

Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

1.2. Policy area(s) concerned in the ABM/ABB structure²⁹

Public health.

The costs will be covered with the envelope of the Health for Growth Programme 2014-2020.

1.3. Nature of the proposal/initiative

The proposal/initiative relates to **a new action**

The proposal/initiative relates to **a new action following a pilot project/preparatory action**³⁰

The proposal/initiative relates to **the extension of an existing action**

The proposal/initiative relates to **an action redirected towards a new action**

1.4. Objectives

1.4.1. *The Commission's multiannual strategic objective(s) targeted by the proposal/initiative*

The proposal aims to promote public health and research across the EU through providing for harmonized rules on the authorisation and conduct of clinical trials.

1.4.2. *Specific objective(s) and ABM/ABB activity(ies) concerned*

Specific objective No. 1: Electronic 'EU portal' and "EU database" for submission for requests for authorisation of clinical trials, and follow-up.

Specific objective No. 2: Update of the 'Clinical trial module' of the existing EudraVigilance database to ensure processing of safety reports during clinical trials.

Specific objective No. 3: A cooperation system amongst Member States in assessing an application for the authorisation of a clinical trial.

²⁹

ABM: Activity-Based Management – ABB: Activity-Based Budgeting.

³⁰

As referred to in Article 49(6)(a) or (b) of the Financial Regulation.

Specific objective No. 4: A mechanism of 'system inspections' of third countries' regulatory systems for clinical trials.

ABM/ABB activity(ies) concerned

Public health

1.4.3. *Expected result(s) and impact*

Specify the effects which the proposal/initiative should have on the beneficiaries/groups targeted.

Effects on sponsors of clinical trials (both 'industry sponsors' and 'non-commercial sponsors'): Reduction in administrative burdens for submitting applications for clinical trials and substantial modifications.

Effects on patients and health systems: Quicker access to new and innovative medicines and treatments.

1.4.4. *Indicators of results and impact*

Specify the indicators for monitoring implementation of the proposal/initiative.

- Number of clinical trials applied for in the EU, as well as the number of subjects;
- Number of multinational clinical trials applied for in the EU, as well as the number of subjects;
- Number of days between finalisation of the protocol and 'first patient in';
- Level of administrative costs presenting administrative burdens, and of operational costs of clinical trials conducted in the EU; and
- Number of clinical trials conducted outside the EU for generating data referred to in the request for authorisation of a clinical trial or a medicinal product.

1.5. **Grounds for the proposal/initiative**

1.5.1. *Requirement(s) to be met in the short or long term*

The Clinical Trials Directive is criticised by all stakeholders (ranging from patients to researchers and industry) for having caused a significant decline in the attractiveness of patient-oriented research and related studies in the EU. Indeed, the number of clinical trials applied for in the EU has fallen from 5028 (2007) to 3800 in 2011. This trend greatly reduces Europe's competitiveness in the field of clinical research and, thus, has a negative impact on the development of new and innovative treatments and medicines.

It is required to address this trend and these criticisms.

1.5.2. *Added value of EU involvement*

Harmonised rules open up the possibility of referring to the results and findings of clinical trials in applications for an authorisation for placing a medicinal product on the Union market, including subsequent variations and extensions of the marketing authorisation.

This is critically important in the case of clinical trials because practically every larger clinical trial is performed in more than one Member State.

An additional factor is that medicinal products intended for research and development trials are excluded from the Community Code for medicinal products for human use. These products may have been produced in a different Member State from that where the clinical trial is conducted. Thus, these products do not benefit from the secondary Union law ensuring their free movement while maintaining a high level of protection of human health.

1.5.3. Lessons learned from similar experiences in the past

In the area of regulation of medicines, since 1975 there are mechanisms in place to facilitate the authorisation of a medicinal product in the internal market. This experience has proven highly successful. Some elements of the present initiative build on the experiences made in the area of the authorisation of medicines.

On the other hand, the Clinical Trials Directive of 2001, which has not provided for any cooperation mechanism between Member States, has been in parts a negative example not to be followed.

1.5.4. Coherence and possible synergy with other relevant instruments

Synergy expected with the revision of the legislation on 'medical devices': this legislation provides for a similar 'EU portal' for 'clinical investigations' (clinical research with medical devices) as is planned for clinical trials.

1.6. Duration and financial impact

Proposal/initiative of **limited duration**

- Proposal/initiative in effect from [DD/MM]YYYY to [DD/MM]YYYY
- Financial impact from YYYY to YYYY

Proposal/initiative of **unlimited duration**

- Implementation with a start-up period from 2014 to 2016 (the start-up period is the time between date of entry into force of the Regulation, i.e. 20 days after its publication, and the date of application of the Regulation: During this time all implementation measures have to be taken by the Commission in order to ensure that the Regulation can function on the day of application of the Regulation),
- followed by full-scale operation.

1.7. Management mode(s) envisaged³¹

Centralised direct management by the Commission

Centralised indirect management with the delegation of implementation tasks to:

- executive agencies
- bodies set up by the Communities³²
- national public-sector bodies/bodies with public-service mission
- persons entrusted with the implementation of specific actions pursuant to Title V of the Treaty on European Union and identified in the relevant basic act within the meaning of Article 49 of the Financial Regulation

Shared management with the Member States

Decentralised management with third countries

Joint management with international organisations (*to be specified*)

If more than one management mode is indicated, please provide details in the "Comments" section.

Comments

³¹ Details of management modes and references to the Financial Regulation may be found on the BudgWeb site: http://www.cc.cec/budg/man/budgmanag/budgmanag_en.html

³² As referred to in Article 185 of the Financial Regulation.

2. MANAGEMENT MEASURES

2.1. Monitoring and reporting rules

Specify frequency and conditions.

The Commission has established mechanisms for working with the Member States to monitor implementation of the EU acquis in the area of pharmaceutical and clinical trials regulation. Notably, the 'Pharmaceutical Committee' is going to provide the forum to monitor and assess the application of the new Regulation.

2.2. Management and control system

2.2.1. Risk(s) identified

The EU portal becomes too complex and does not meet the requirements of the users (Member States and sponsors). Thus, the EU portal would not have the simplifying effect it intends to achieve.

2.2.2. Control method(s) envisaged

Close and regular contacts with the developers of the EU portal.

Repeated meetings with stakeholders and Member States to ensure that the EU portal meets users' needs.

2.3. Measures to prevent fraud and irregularities

Specify existing or envisaged prevention and protection measures.

In addition to the application of all regulatory control mechanisms, DG SANCO will devise an anti-fraud strategy in line with the Commission's new anti-fraud strategy (CAFS) adopted on 24 June 2011 in order to ensure *inter alia* that its internal anti-fraud related controls are fully aligned with the CASF and that its fraud risk management approach is geared to identify fraud risk areas and adequate responses. Where necessary, networking groups and adequate IT tools dedicated to analysing fraud cases related to the financing implementing activities of the Clinical Trials Regulation will be set up. In particular a series of measures will be put in place such as:

- decisions, agreements and contracts resulting from the financing implementing activities of the Clinical Trials Regulation will expressly entitle the Commission, including OLAF, and the Court of Auditors to conduct audits, on-the-spot checks and inspections;
- during the evaluation phase of a call for proposals/tender, the proposers and tenderers are checked against the published exclusion criteria based on declarations and the Early Warning System (EWS);
- the rules governing the eligibility of costs will be simplified in accordance with the provisions of the Financial Regulation;
- regular training on issues related to fraud and irregularities is given to all staff involved in

contract management as well as to auditors and controllers who verify the beneficiaries' declarations on the spot.

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected

- Existing expenditure budget lines

In order of multiannual financial framework headings and budget lines.

Heading of multiannual financial framework	Budget line	Type of expenditure	Contribution			
	Number [Description: Public Health Program]	Diff./non-diff. (33)	from EFTA ³⁴ countries	from candidate countries ³⁵	from third countries	within the meaning of Article 18(1)(aa) of the Financial Regulation
3B	17.03.XX	Diff./non-diff.	YES/NO	YES/NO	YES/NO	YES/NO

- New budget lines requested

In order of multiannual financial framework headings and budget lines.

Heading of multiannual financial framework	Budget line	Type of expenditure	Contribution			
	Number [Heading.....]	Diff./non-diff.	from EFTA countries	from candidate countries	from third countries	within the meaning of Article 18(1)(aa) of the Financial Regulation
[...]	[XX.YY.YY.YY] [...]	[...]	YES/NO	YES/NO	YES/NO	YES/NO

³³ Diff. = Differentiated appropriations / Non-diff. = Non-Differentiated Appropriations

³⁴ EFTA: European Free Trade Association.

³⁵ Candidate countries and, where applicable, potential candidate countries from the Western Balkans.

3.2. Estimated impact on expenditure

3.2.1. Summary of estimated impact on expenditure

EUR

Heading of multiannual financial framework:	Number 3B	Public Health Program
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DG: SANCO			Year 2014 ³⁶	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020 and following years	TOTAL
• Operational appropriations										
Number of budget line: 17.03.XX	Commitments	(1)	895.000	1.082.000	238.000	193.000	180.000	184.000	187.000	2.959.000
	Payments	(2)	447.000	998.000	671.000	232.000	175.000	184.000	187.000 + 65.000	2.959.000
Number of budget line	Commitments	(1a)								
	Payments	(2a)								
Appropriations of an administrative nature financed from the envelope for specific programmes ³⁷										
Number of budget line: 17.01.04.02		(3)	57.000	58.000	119.000	121.000	124.000	126.000	129.000	734.000
TOTAL appropriations	Commitments	=1+1a +3	952.000	1.140.000	357.000	314.000	304.000	310.000	316.000	3.693.000

³⁶ All prices are current prices.

³⁷ Technical and/or administrative assistance and expenditure in support of the implementation of EU programmes and/or actions (former "BA" lines), indirect research, direct research.

for DG SANCO	Payments	=2+2a +3	504.000	1.056.0 00	790.000	353.000	299.000	310.000	316.000 + 65.000	3.693.000
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• TOTAL operational appropriations	Commitments	(4)	895.000	1.082.0 00	238.000	193.000	180.000	184.000	187.000	2.959.000
	Payments	(5)	447.000	998.000	671.000	232.000	175.000	184.000	187.000 + 65.000	2.959.000
• TOTAL appropriations of an administrative nature financed from the envelope for specific programmes		(6)	57.000	58.000	119.000	121.000	124.000	126.000	129.000	734.000
TOTAL appropriations under HEADING SANCO of the multiannual financial framework	Commitments		952.000	1.140.0 00	357.000	314.000	304.000	310.000	316.000	3.693.000
	Payments		504.000	1.056.0 00	790.000	353.000	299.000	310.000	316.000 + 65.000	3.693.000

If more than one heading is affected by the proposal / initiative:

• TOTAL operational appropriations	Commitments	(4)								
	Payments	(5)								
• TOTAL appropriations of an administrative nature financed from the envelope for specific programmes		(6)								
TOTAL appropriations under HEADINGS 1 to 4 of the multiannual financial framework (Reference amount)	Commitments	=4+ 6								
	Payments	=5+ 6								

Heading of multiannual financial framework:	5	" Administrative expenditure "
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EUR

		Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020 and following years	TOTAL
DG: SANCO									
• Human resources ³⁸		222.000	222.000	857.000	857.000	857.000	857.000	857.000	4.730.000 ³⁹
• Other administrative expenditure				87.000	88.000	90.000	92.000	94.000	451.000
TOTAL DG SANCO ⁴⁰	Appropriations			87.000	88.000	90.000	92.000	94.000	451.000
TOTAL appropriations under HEADING 5 of the multiannual financial framework ⁴¹	(Total commitments = Total payments)			87.000	88.000	90.000	92.000	94.000	451.000

³⁸ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE with date of application) are going to be re-deployed from within DG SANCO.

³⁹ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'total' for Heading 5.

⁴⁰ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'total DG SANCO'.

⁴¹ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'total' for Heading 5.

EUR

		Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020 and following years	TOTAL
TOTAL appropriations under HEADINGS 1 to 5 of the multiannual financial framework	Commitments	952.000	1.140.0 00	444.000	402.000	394.000	402.000	410.000	4.144.000
	Payments	504.000	1.056.0 00	877.000	441.000	389.000	402.000	410.000 + 65.000	4.144.000

3.2.2. *Estimated impact on operational appropriations*

- The proposal/initiative does not require the use of operational appropriations
- The proposal/initiative requires the use of operational appropriations, as explained below:

Commitment appropriations in EUR

Indicate objectives and outputs	OUTPUTS																TOTAL	
	Year 2014	Year 2015	Year 2016	Year 2017	Year 2108	Year 2019	Year 2020 and following years											
↓	Type of output	Average cost of the output	Number	Cost	Number	Cost	Number of outputs	Cost	Number of outputs	Cost	Number	Cost	Number	Cost	Number	Cost	Total number of outputs	Total cost
<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> SPECIFIC OBJECTIVE No 1 Electronic 'EU portal' and "EU database" for submission for requests for authorisation of clinical trials, and follow-up </div>																		
- Output	IT Portal		1	595.00	1	782.00	1	238.00	1	193.00	1	180.0	1	184.00	1	187.00	7	2.359.00
Sub-total for specific objective N°1			1	595.00 0	1	782.00 0	1	238.00 0	1	193.00 0	1	180.0 00	1	184.00 0	1	187.00 0	7	2.359.00 0
<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> SPECIFIC OBJECTIVE No 2 Update of the 'Clinical trial module' of the existing EudraVigilance database to ensure processing of safety reports during clinical trials. </div>																		
- Output	IT update		1	300.00	1	300.00											2	600.000
Sub-total for specific objective N°2			1	300.00	1	300.00											2	600.000

		0		0													
- Output	Meetings																
- Output	System inspector																
TOTAL COST		2	895.00 0	2	1.082. 000	1	238.00 0	1	193.00 0	1	180.0 00	1	184.00 0	1	187.00 0	9	2.959.00 0

3.2.3. Estimated impact on appropriations of an administrative nature

3.2.3.1. Summary

- The proposal/initiative does not require the use of administrative appropriations
- The proposal/initiative requires the use of administrative appropriations, as explained below:

	Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020 and following years	TOTAL
--	-----------	-----------	-----------	-----------	-----------	-----------	-------------------------------	-------

HEADING 5 of the multiannual financial framework								
Human resources ⁴²	222.000	222.000	857.000	857.000	857.000	857.000	857.000	4.730.000 ₄₃
Other administrative expenditure			87.000	88.000	90.000	92.000	94.000	451.000
Subtotal HEADING 5 of the multiannual financial framework ⁴⁴			87.000	88.000	90.000	92.000	94.000	451.000

Outside HEADING 5⁴⁵ of the multiannual financial framework								
Human resources								
Other expenditure of an administrative nature	57.000	58.000	119.000	121.000	124.000	126.000	129.000	734.000
Subtotal outside HEADING 5 of the multiannual financial framework	57.000	58.000	119.000	121.000	124.000	126.000	129.000	734.000

⁴² In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO.

⁴³ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'subtotal' for Heading 5.

⁴⁴ In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'subtotal' for Heading 5.

⁴⁵ Technical and/or administrative assistance and expenditure in support of the implementation of EU programmes and/or actions (former "BA" lines), indirect research, direct research.

TOTAL⁴⁶	57.000	58.000	206.000	209.000	214.000	218.000	223.000	1.185.000
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⁴⁶

In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO. Consequently, the costs for human resources are not added in the 'total' of administrative expenditure.

3.2.3.2. Estimated requirements of human resources

- The proposal/initiative does not require the use of human resources⁴⁷
- The proposal/initiative requires the use of human resources, as explained below:

	Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020 and following years	TO
–								
17 01 01 01 (Headquarters and Commission's Representation Offices) ⁴⁸	1.75 FTEc	1.75 FTE	6.75 FTE					
XX 01 01 02 (Delegations)								
XX 01 05 01 (Indirect research)								
10 01 05 01 (Direct research)								
XX 01 02 01 (CA, INT, SNE from the "global envelope")								
XX 01 02 02 (CA, INT, JED, LA and SNE in the delegations)								
XX 01 04 yy ⁴⁹ – at Headquarters ⁵⁰								
– in delegations								
XX 01 05 02 (CA, INT, SNE - Indirect research)								
10 01 05 02 (CA, INT, SNE - Direct research)								
Other budget lines (specify)								
TOTAL								

XX is the policy area or budget title concerned.

The human resources required will be met by staff from the DG who are already assigned to management of the action and/or have been redeployed within the DG, together if necessary with any additional allocation which may be granted to the managing DG under the annual allocation procedure and in the light of budgetary constraints.

Description of tasks to be carried out:

Officials and temporary agents	General questions in relation to the authorisation procedure for clinical trials. Preparation, chairing and follow-up of the relevant expert group. 'System inspections' in third countries.
External personnel	

⁴⁷ **In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO.**

⁴⁸ **In accordance with the impact assessment report, the necessary additional human resources (1.75 FTE + 5 FTE) are going to be re-deployed from within DG SANCO.**

⁴⁹ Under the ceiling for external personnel from operational appropriations (former "BA" lines).

⁵⁰ Essentially for Structural Funds, European Agricultural Fund for Rural Development (EAFRD) and European Fisheries Fund (EFF).

3.2.4. Compatibility with the current multiannual financial framework

- Proposal/initiative is compatible the 2014-2020 multiannual financial framework.
- Proposal/initiative will entail reprogramming of the relevant heading in the multiannual financial framework.

Explain what reprogramming is required, specifying the budget lines concerned and the corresponding amounts.

- Proposal/initiative requires application of the flexibility instrument or revision of the multiannual financial framework⁵¹.

Explain what is required, specifying the headings and budget lines concerned and the corresponding amounts.

3.2.5. Third-party contributions

- The proposal/initiative does not provide for co-financing by third parties
- The proposal/initiative provides for the co-financing estimated below:

Appropriations in EUR million (to 3 decimal places)

	Year N	Year N+1	Year N+2	Year N+3	... enter as many years as necessary to show the duration of the impact (see point 1.6)			Total
<i>Specify the co-financing body</i>								
TOTAL appropriations cofinanced								

⁵¹ See points 19 and 24 of the Interinstitutional Agreement.

3.3. Estimated impact on revenue

- Proposal/initiative has no financial impact on revenue.