Agence nationale de sécurité du médicament et des produits de santé

Notice for Sponsors

The installation and control in France of clinical trials relating to medical devices and in vitro diagnostic medical devices

This document is intended to help the participants in biomedical research. You can address your comments, questions and remarks to the following email address: EC.DM-COS@ansm.sante.fr

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Contents

List of abbreviations

AEC	Autorisation d'essai clinique / Authorisation of clinical trial
ANSM	Agence nationale de sécurité du médicament et des produits de santé / National Drug and Health Products Safety Agency
AMS	Autorisation de modification substantielle / Authorisation of substantial modification
BI	Brochure pour l'investigateur / Booklet for the investigator
CCPPRB	Comité consultatif de protection des personnes dans la recherche biomédicale /Consultative Committee for public protection (CPPP) in biomedical research
CEB	Collection d'échantillons biologiques / Collection of biological samples
CPP	Comité de protection des personnes / Committee for public protection
CSP	Code de la santé publique / Code of public health
DA	Dossier administratif / Administrative file
DEC	Dossier sur l'essai clinique / la recherche /Dossier on the clinical trial/research
DEDIM	Direction de l'évaluation des dispositifs médicaux et des dispositifs médicaux de diagnostic in vitro /Direction of the evaluation of medical devices and the medical devices of in vitro diagnostic
DGS	Direction générale de la santé / Directorate-General of health
DGSNR	Direction générale de la sûreté nucléaire et de la radioprotection / Directorate-General of nuclear safety and protection against radiation
DT	Dossier technique / Technical dossier
EC.	Essai clinique / Clinical trial

E.I.	Effet indesirable / Adverse effect
EIG	Effet indésirable grave / Serious adverse effect
EIGI	Effet indésirable grave et inattendu / serious and unexpected adverse effect
GTSV	Groupe de travail de sécurité virale / Working group of viral safety
OJ	Journal officiel (de la République française) / Official Journal (of the French Republic)
OJ of the European Communities	Journal officiel des Communautés européennes / Official Journal of the European Communities
GMO	Organisme génétiquement modifié / Genetically modified organism
RAR	Rapport annuel de sécurité / Annual safety report
UEC	Unité essais cliniques / clinical investigation Unit

Introduction

Legislative and legal provisions

The implementation of clinical trials in France has been restricted since 1988 by law n° 88-1138 of December 20, 1988 (known as the "Huriet - Sérusclat" law) and its decree of application.

This legislative and legal provision was modified by the transposition in French law of European directive 2001/20/EC of April 4, 2001 relating to the application of good clinical practice in the control of clinical trials of drugs for human use.

During this transposition, new provisions aimed at standardising the level of public protection for whatever the health product biomedical research (RBM) is. The regulation of RBM over medical devices and medical devices in vitro diagnostic was thus modified.

The new provisions were introduced by law n° 2004-8 06 of August 9, 2004 relating to public health policy and its decree of application n° 2006-477 of April 26, 2006, and by the decrees and decisions relative to it.

The whole texts came into force as from August 27, 2006.

These legislative and legal texts are available on the Internet site of ANSM at the following address: www.ansm.sante.fr (headings "Clinical trials"/ "medical devices & medical devices of in vitro diagnostic").

General information relating to biomedical research is also available on the Internet site of the Ministry for Health and Solidarity (www.sante.gouv.fr).

Scope and object of the notice for sponsors

This notice for sponsors only concerns interventional biomedical research relating to medical devices and in vitro diagnostic medical devices (cf §3 of "General Standards" of this notice for sponsors).

It aims at facilitating the interpretation of the new legislative and legal provisions applicable to this kind of research in France and to specify, on a practical level, the expectations of the French Agency of Medical Safety (ANSM) regarding health products in this context.

It is for the use of the sponsors of biomedical research, of consultant research office (CRO) elected by these sponsors, to applicants, and any person or organisation likely to be concerned by the implementation of these new legal provisions.

Therefore it does not concern:
- trials relating to other products coming under the responsibility of ANSM, as defined in article L. 5311-1 of the Code of Public Health (CSP) (eg: cosmetic products and drugs) and trials not related to health products ;
- non interventional trials (cf. §1 of "General Standards" of this notice for sponsors), those not entering the field of application of law n° 2004-806 of Augu st 9, 2004;
- trials aimed at evaluating ordinary care, as defined in the 2° of the article L. 1121-1 of the CSP.

This notice to sponsors does not have for aim to deal with the aspects of the new legal provisions exhaustively relating to committees of public protection (CPPP) or their expectations on a practical level.

General standards

The Law provides that biomedical research relating to a medical device or in vitro diagnostic medical device can be set up only after a favourable notification from the CPP and authorisation from ANSM (L.1121-4 article of the law of public health of the code of public health).

1. Definition of a non interventional clinical trial

References

Article L. 1121-1, 1°, of the CSP
Article R. 1121-2 of the CSP

These are clinical studies in which all acts are practiced and products used in a usual manner, the medical device (DM)or in vitro diagnostic medical device (DM-DIV) is used in accordance with the instruction for use or manual, without any additional or unusual procedure of diagnostic or monitoring. The assignment of the patient to a given medical therapy is not fixed in advance by a trial protocol, it concerns current practice, the decision to use DM or DM-DIV is clearly dissociated from including the patient in the study.

2. Definition of ordinary care trial

Reference

Article L. 1121-1 of the CSP to the 2°
Article R. 1121-3 of the CSP

The trials aiming at evaluating ordinary care do not relate to drugs, all the acts are practiced and the products used in a usual way but particular methods of monitoring are envisaged by a protocol, obligatorily subjected to the opinion of the Committee for public protection (CPP). This protocol also specifies the corresponding information for those concerned.

The objective of these trials is to evaluate acts, combinations of acts or medical strategies for prevention, diagnostic or treatment which are of current practice, i.e. the subject of a professional consensus, in agreement with their indications.
Thus the following trials do not concern this category:
1° those that relate to innovating techniques or therapies or therapies considered as obsolete;
2° those which relate to the evaluation of an innovating combination of acts or products, even if each one of those taken separately is of current use.
3° research which relates to a comparison of medical therapeutic strategies, if one of the compared strategies can be regarded as superior to the other in terms of safety and effectiveness.
The particular methods of monitoring implemented in the research of ordinary care involve only negligible risks and constraints for persons involved in the research.
Correctly informing these persons is the subject of a written document submitted to the Committee for public protection (CPP) concerned.

3. Definition of an interventional clinical trial.

The scope of application of the provisions of law n° 2004-806 of August 9 2004 is limited to trials designated “interventional”.

The interventional clinical trial is distinct from the non interventional clinical trial and ordinary care trial.

The interventional clinical trials bearing on a medical device (DM) are understood as any clinical trial or clinical investigation of one or more medical devices aiming at determining or confirming their performances or highlighting their adverse effects and at evaluating if these constitute risks taking into consideration the performances imputed to the device.

In France, these provisions imply that ANSM evaluates the requests for authorisations of clinical trials (AEC), before their beginning and within 60 days maximum (this delay may be reduced for certain trials). This authorisation regimen is in place instead of the previous declaratory mode in force for overall trials.

A trial can begin only after obtaining both an authorisation for the trial granted by ANSM and a favourable opinion from the Committee for public protection (CPP).

The applicant

One understands by applicant the person or the organisation who is charged of the submission of the request for AEC or for substantial modification to ANSM or the request for approval from CPPP. The applicant can be:
- the sponsor,
- or the legal representative of the sponsor,
- or the person or organisation delegated by the sponsor or its legal representative to submit the request (e.g. service firm).

The sponsor

References

Article L. 1121-1 of the CSP

The sponsor is the person or entity who takes the initiative of biomedical research on human beings, which ensures the management of this research, and which verifies that its financing is planned.

When several persons or entities take the initiative of undertaking the same research, a single sponsor must be designated to assume the responsibility for the course of the research on national territory.

A sponsor can be described as “commercial” or “non commercial”, for a given research project, according to the finality of this project (cf below).

. Definition of a “commercial” sponsor

One understands by “commercial” sponsor, any person or entity taking the initiative to undertake biomedical research which is registered, at the moment of submission of the request for AEC, and which does not fit the definition of an institutional sponsor.**1[1]**

. Definition of an institutional sponsor

By “institutional” sponsor, is understood any person or entity that takes the initiative in undertaking biomedical research whose implementation, at the time of the submission of the request for AEC, is not related to obtaining an EC marking. It is of an organisation or a person which is non profit-making.
In France, this can be a public research organisation , a university, a publicly-owned health establishment or a private health establishment in which is part of the public hospital public service, a publicly-owned establishment or any other person or entity which is a non profit-making.2[2]. These are also denoted “non commercial” or “academic” sponsors.
- the owner of the data from the clinical trial is this entity;
- at the moment of the request for AEC, there is no commitment binding the sponsor and a third party authorising it to use this data for marketing purposes.

It should be noted that a sponsor usually described as “institutional” can, in certain cases, be qualified as a “commercial” sponsor for a given clinical trial, if, within the framework of the trial, the sponsor’s objective is mercantile.

The sponsor’s legal representative

Reference

Article L. 1121-1 of the CSP

The sponsor may be established outside France.

In this case:

If the sponsor is established outside the European Community, a legal representative has to be named.

This legal representative must be established in the European Community (eg: European subsidiary company of a laboratory whose head office is established outside the European Community) and must respect all French legislative and legal provisions.

The legal representative takes on the responsibilities of the sponsor and then, in particular, transmits the dossier of request for AEC on behalf of the sponsor to ANSM.

As with the sponsor, the legal representative can be a person or legal entity. This representative himself can itself delegate certain functions related to research, such as the transmission of the dossier for request for AEC, to another person or another organism which will have already been designated his responsibilitiy remaining entire.

1[1] Definition resulting from the footnote n°6 for the form for request for AEC/CPP approval (Cf. annexes “Form of request for AEC/CPP”)
2[2] Cf. article L. 1123-8, subparagraph 8, of the CSP

The legal representative, who is distinct from the sponsor, cannot consist of a simple P.0. box.

If a sponsor, established outside the territory of the European Community, carries out several trials on European territory, this sponsor, if it wishes , can name a different legal representative for each clinical trial of which it assumes promotion.

 If a sponsor is established outside France but within the European Community, it must respect all French legislative and legal provisions. It cannot designate a legal representative but can however delegate some of its functions to another person or another organisation.

. The person or organisation delegated by the sponsor or its legal representative

As mentioned in the above paragraphs, the sponsor or its legal representative can delegate the submission of the dossier of request for AEC to another person or organism on which consequently becomes the applicant.

Practical information

Before sending the dossier of request for authorisation for biomedical research on a medical device or in vitro diagnostic medical device, the sponsor must connect to the website to obtain an identification for the trial (ID RCB). To this end, the sponsor follows the procedure indicated on ANSM's web site (ictaxercb.ANSM.fr), thus obtaining the registration number related to the research in question. This figure identifies the research and must be mentioned on all the documents corresponding to this research. After that, the sponsor thus obtains a document in proof which must be included in the dossier of request for aprovel from ANSM and the request for opinion from the CPP.

The sponsor is asked to quote this registration figure in any later correspondence.

1 Beginning the trial

Legislative and regulatory references			
	Title summary	Complete title	Publication
RIGHT FRENCH	Law of August 9, 2004	Law n° 2004-806 of August 9, 2004, modified, relating to public health policy	August 11, 2004
	Decree of April 26, 2006	Decree n° 2006-477 of 26 April 2006 modifying the 1st chapter of title II of the 1st book of the first part of the code of public health relating to biomedical research (regulations)	April 27, 2006
	Decree AEC	Decree of 16 August 2006 fixing the contents, the format and the methods of presentation to the French Agency for Medical Safety of products of health of the dossier for request for authorisation of biomedical research relating to a medical device or in vitro diagnostic medical device	August 26, 2006
	Decree CPP	Decree of 16 August 2006 fixing the contents, the format and the methods of presentation of the dossier of request for authorisation from the committee of public protection of a biomedical research project relating to a medical device or in vitro diagnostic medical devices	August 26, 2006
	Decree protocol	Decree of 16 August 2006 relating to the contents and the methods of presentation of a protocol of biomedical research relating to a medical device or in vitro diagnostic medical devices	August 26, 2006
	Decree BI	Decree of 16 August 2006 relating to the contents and the methods of presentation of booklets for the investigator in biomedical research relating to medical devices and in vitro diagnostic medical devices	August 26, 2006
	Decree repertory		To appear

1.1 Preamble

Legislative and legal references
Articles 1 and 2 of decree AEC

Before the setting up of biomedical research relating to a DM or DM-DIV, the applicants must:
- obtain the registration number for research from ANSM;
- submit a dossier of request for authorisation to ANSM and a file of request to the CPP.

In all cases, a trial can begin only after obtaining both the authorisation for the trial granted by ANSM and a favourable opinion from the CPP.

1.2 Request for authorisation for a clinical trial (AEC) at ANSM

The contents of the dossier of request for AEC addressed to ANSM as well as the methods relating to its submission and its instruction, up to the stage of decision of authorisation or refusal of authorisation for research, are detailed hereafter.

1.2.1 Contents and presentation of the file

1.2.1.1 Contents

Legislative and legal references
Article R. 1123-30 of the CSP Decree AEC

The dossier of request for AEC comprises 4 parts and enclosures.

1.2.1.1.1 Part 1: administrative file (DA)

1.2.1.1.2 Part 2: biomedical research file

1.2.1.1.3 Part 3: technical file (DT)

The DT presents the data relating to products used within the framework of the research.

It must be submitted for:

- each medical device (DM) or in vitro diagnostic medical device (DM-DIV) on which research is to be carried out,
- as for, if necessary, any other product used within the framework of the research such as, for example, a drug.

1.2.1.1.3.1 Technical dossier of the medical device (DM) or in vitro diagnostic medical device (DM-DIV) on which research is to be carried out

The DT can be complete or simplified.

1.2.1.1.3.2 File relating to any other product studied in the research

A file must also be provided for any other product studied within the framework of the research relating to a medical device (DM) or a in vitro diagnostic medical device (DM-DIV). This could be for example a drug used as a reference in the research.

1.2.1.1.4 Part 4: copy of the final notification of the CPP

The final notification of the CPP must be joined to the dossier, if this notification is available.

However, if only an ordinary letter from the CPP is available at the moment of depositing the dossier of request for AEC, it is strongly recommended to send a copy of it to ANSM.

1.2.1.1.5 Enclosures

The elements to be included in the dossier for request for AEC are essential for its admissibility.

1.2.1.1.5.1 Declaration relating to the constitution of a collection of biological samples

Legislative and legal references
Article and L. 1123.7, L. 1123-12 and L. 1243-3 of the CSP Decree AEC

It is understood by “collection of human biological samples” (CEB), the collecting together, to scientific ends, of biological samples taken from a group of people identified and selected according to the clinical or biological characteristics of one or more members of the group, as well as derivatives of these samples.

When a CEB is only constituted for the needs of biomedical research, this collection must be declared with ANSM and not with the Ministry in charge of Research.

It should be noted that within the framework of a clinical trial, the constitution of a CEB is not the subject of authorisation but only of one declaration enclosed in the dossier of request for AEC.

1.2.1.1.5.2 Acceptance or refusal of registering of the research in the repertory of authorised research.

Legislative and legal references
Article L. 1121-15 of the CSP Article R. 1121-17 of the CSP Decree AEC Decree repertory

After publication and implementation of the decree determining the contents of the repertory of authorised clinical trials bearing on medical devices (DM) or medical devices of in vitro diagnostic (DM-DIV), ANSM will set up and will diffuse this repertory.

The methods of registration of research in this repertory will be then detailed in the chapter “Repertory of authorised clinical trials” of this notice for sponsors and its contents will be specified in a table called “contents of the repertory of authorised biomedical research”.

It will then be imperative that the sponsor encloses with its request for AEC its agreement or refusal (justified) of registration in the repertory of EC which is the subject of the request.

It should be noted that the agreement or the refusal of registration of research in the repertory, formulated by the applicant at the time of request for AEC, will not be an element taken into account within the framework of the process of evaluation of the request for AEC.

Thus, the agreement or refusal will have no impact on the decision taken by ANSM to authorise or not authorise a clinical trial. Indeed, a possible refusal of registration on behalf of the applicant and the applicant’s management will not delay the delivery of the AEC.

1.2.1.2 Language

The following elements of the dossier of request for authorisation of a trial addressed to ANSM, or enclosed with this file, must be written in French:

- a summary of the protocol;
- the elements to be published, in French, in the repertory (form “contents of the repertory of authorised biomedical research”).

The other components of the dossier of request for AEC addressed to ANSM can be written in French or English.

The non respect of these instructions constitutes a reason for non admissibility.

1.2.1.3 Presentation

The dossier is presented according to the structure described in the decree related to the dossier of request for AEC.

Respecting this format of presentation makes it possible to guarantee optimised management of the dossier by ANSM, and thus to decrease the time of instruction of it.

1.2.2 Methods of submission of the dossier

1.2.2.1 Who deposits the dossier?

Legislative and legal references
Articles L. 1121-1 and L. 1123-6 of the CSP Decree AEC

The dossier of request for AEC is addressed to ANSM by the applicant who can be:

1. the sponsor,
2. or the legal representative of the sponsor,
3. or the person or organisation delegated by the sponsor or his legal representative to submit the request.

1.2.2.2 When should the dossier be submitted?

Legislative and legal references
Article L. 1121-4 of the CSP

The dossiers are deposited on working days.

Chronology of submission of the files to ANSM and the CPP:
The applicant is able to deposit the file at ANSM:

- before the request for notification of the CPP;
- at the same time as the request for notification of the CPP;
- or after having obtained the notification of the CPP.

1.2.2.3 How should the dossier be submitted?

Legislative and legal references
Decree AEC

1.2.2.3.1 Submitting electronically

The dossier of request for AEC is transmitted to ANSM electronically, according to the following methods:

- by email, only for non bulky files i.e. of less than 5 megabytes.

The files transmitted by email must be addressed to the following address:
EC.DM-COS@ansm.sante.fr a file addressed to another address can not be dealt with, even if at this other address an agent of ANSM receives it.

This address **EC.DM-COS@ansm.sante.fr** is to be used for sending all documents and exchanges of information relating to clinical trials of medical devices and medical devices of in vitro diagnostic

(request for initial authorisation, responses to correspondence of ANSM, requests for authorisation of substantial modification, declaration of serious undesirable events etc.) to ANSM.

It is very important to fill in the 'subject' line of the email correctly with the following elements: biomedical research reference, type of request or correspondence.

- **or by sending a CDROM**. For bulky files, i.e. over 5 megabytes, a CDROM is necessary.

1.2.2.3.2 Dossiers or parts of dossiers transmitted by post or messenger

When the use of email is not possible, the dossier can be sent by registered post with proof of delivery or by messenger.

They must be addressed to:

Agence nationale de sécurité du médicament et des produits de santé (ANSM)
Direction des dispositifs médicaux thérapeutiques et des cosmétiques
Essais cliniques
143-147 Boulevard Anatole France
93285 Saint-Denis cedex

Three copies must be sent.

1.2.3 Instruction of the file by ANSM

Legislative and legal references
Article R. 1123-32 of the CSP Decree AEC

The evaluation of the file by ANSM consists of:
- checking that the dossier is complete (a technical and legal obligation for admissibility),
- the technical assessment.

1.2.3.1 Admissibility of the request/acknowledgement of delivery

1.2.3.1.1 Criteria of admissibility

Concerning the evaluation of the admissibility of a file, the following points are examined in particular:

- coordinating the various elements of the dossier necessary to the scientific evaluation with:
- the type of product (e.g. viral safety data provided if the product is of biological origin);
- the type of dossier (e.g. simplified file);
- coordinating the various elements of the dossier necessary for legislative and legal requirements;
  - the enclosure of the necessary administrative elements;
  - the number of copies received in the case of transmission by postal mail;
  - with regard to the instructions given relating to the language to be used.

1.2.3.1.2 Delay for evaluation of admissibility

The delay for the evaluation of the admissibility of the dossier is included within the evaluation delay at ANSM.

1.2.3.1.3 Notification of the admissibility of the dossier/acknowledgment of delivery

ANSM acknowledges receipt of any request for AEC which is addressed to it, as soon as the admissibility of the file has been evaluated.

This acknowledgment of delivery is duly filled out from the part of form 2 headed

« Courrier de demande d'autorisation de recherche biomédicale portant sur un dispositif médical ou dispositif médical de diagnostic in vitro auprès de l'Agence Nationale de sécurité du médicament et des produits de santé des produits de santé »

This acknowledgment of delivery specifies if the dossier of request is:

-complete,
or
-incomplete.

The acknowledgment of delivery is addressed by fax or by post .

If the dossier is complete, the correspondence confirms that the date of the beginning of the evaluation of the dossier corresponds to the date of receipt of the complete dossier. It specifies in particular the name of the assessor at ANSM who will be principally in charge of the dossier.

If the initial dossier is incomplete, the sponsor is invited to provide the missing elements of the dossier which are specified, and asked to provide them before a specific date mentioned in the acknowledgment of delivery.
The instruction of the file will be able to start only from the receipt of the complete dossier with ANSM. The sponsor who does not provide the elements requested within the time limits specified will be understood to have withdrawn his request.

ANSM recommends that the sponsor address any questions by email to the following address: **EC.DM-COS@ansm.sante.fr** and in the subject of the email indicate the research registration number obtained from ANSM.

In the case of a non admissible dossier, an email is doubled by the sending of a registered letter with proof of receipt.

Important note:
It is important to note that:
- a receipt issued by the postal service,
- or a receipt delivered to messengers on receipt by ANSM,
- or notifications of receipt by emails, generated automatically by electronic messengers means, do not constitute acknowledgment of delivery and admissibility of the request for AEC as stipulated in R.1123-32 articles of the code of public health and 19 of law n° 2000-321 of April 12, 2000 relating to citizens' rights in their relationships with administrations.

1.2.3.2 Evaluation of dossiers by ANSM

1.2.3.2.1 Organisation

The technical assessment of the dossier is performed by:

- an internal assessment conducted by:
  - -specialised assessors of DEDIM:
    - within the UEC, persons in charge of different therapeutic fields,
    - within the UECM and UND according to field of expertise,
  - -specialised assessors within other departments of ANSM (e.g. Direction of the evaluation of drugs and biological products – DEMEB).

- an external assessments conducted by:
  - -external experts;
  - -groups of experts that the dossier is submitted to, such as:
    - . the group of experts on biomedical research relating to medical devices (DM) working in conjunction with the general manager of ANSM in the case of, for example and in particular, of issues raised requiring a multidisciplinary discussion;
    - . the working group on viral safety (GTSV), for RBM related to medical devices (DM) for which the request for AEC comprises a dossier on viral safety.

According to the nature of the dossiers deposited, the resort to external expertise and the submission of the files to these groups is not systematic.

1.2.3.2.2 Object of technical assessment

The technical evaluation carried out by ANSM relates in particular to:
- the list of reference frameworks applied,
- results of risks analysis ,
- non clinical data,
- clinical data,
- the research protocol.

The technical assessment aims to ensure the safety of medical devices (DM) or medical devices of in vitro diagnostic (DM-DIV) and of the people likely to be involved in the trial, considering, in particular:
- -data documenting the conformity of essential requirements (conformity to applied standards), safety of use (clinical and non clinical data, relevance of risks analysis, estimation of potential risks), and even as regards data documenting quality and safety of use of other products used;
- -the conditions of use of the products used (medical devices (DM) or DM DIV) and other(s) within the framework of the research, as fixed by the protocol of the trial;
- -projected methods of individual follow-up.

Thus the evaluation of the protocol, taking into account of the data available on the medical device(s) (DM) or medical device(s) of in vitro diagnostic (DM-DIV) used, focuses mainly on:
- criteria of inclusion and non inclusion,
- methods of monitoring persons,

- the conformity of certain parts of the protocol to the instructions for use if the DM or DM-DIV has an EC marking (methods of use, criteria of inclusion and non inclusion, precautions for use), including for the reference product,
- modalities of declaration of adverse effects and the possible need to constitute an independent monitoring committee.

The methods of the evaluation carried out by ANSM depend on the class and nature of the DM or DM-DIV which is the subject of the research submitted but also on its degree of innovation. The evaluation is focused on the clinical trial concerned and, within this framework, on safety points. The evaluation can be affected by information resulting from the evaluation of similar clinical trials or related to DM or DM-DIV of the same common denomination for example.

ANSM also can, in certain cases, being brought to express remarks whose content should be taken into account by the sponsor during the submissions of any later requests for trial authorisations.

1.2.3.2.3 Delay of evaluation

1.2.3.2.3.1 Beginning of evaluation

1.2.3.2.3.1.1 Admissible file

The technical assessment begins from the time of reception of the complete file. The delay of evaluation imparted to ANSM covers the period of evaluation of the admissibility of the file as well as that of its technical assessment.

For dossiers initially considered to be non admissible, and which are resubmitted or supplemented by additional information, the beginning of the evaluation corresponds to the date of the receipt of the new submission of a complete dossier.

1.2.3.2.3.1.2 Non admissible file

If the dossier is not admissible, the applicant is informed of the reasons for non-admissibility and is invited to convey the missing parts, as identified in the acknowledgement of reception by ANSM.

For all missing parts sent to ANSM the registration number obtained from ANSM must be specified.

A letter will be addressed to the applicant to inform him of the admissibility or not of the supplemented file.

1.2.3.2.3.2 Duration of evaluation

Caution: The calculation of days is done in calendar days, and thus includes the working days AND public holidays (Saturday, Sunday and public holidays).

The time for instruction of a request for AEC cannot exceed 60 days (period of admissibility included) from the date of the receipt of a complete dossier. However, ANSM has to the option of notifying the applicant of its decision before the expiry of this 60 days deadline.

As an indication, the examination of the application should be carried out according to the following chronology:

- the conclusions of the first evaluation can be notified to the applicant in about 30 days;
- in the event of request for additional information, a response from the applicant is necessary within a delay specified by ANSM (e.g. 40 days if the conclusions of the first evaluation were returned within 30 days);
- and, in this case, the final decision of ANSM regarding the re-trial would be announced in 60 days.

Thus, if the evaluation results in no objection or no request for additional information, the final decision of ANSM could be formulated within 30 days and would then be notified by letter to the applicant.

For trials related to a DM of class I or IIa, other than the devices of long term invasive IIa class, and for the trials related to a DM or DM-DIV, having already been the subject of an authorisation in France, ANSM examines the application for AEC within a period not exceeding 30 days from the date of reception of a complete dossier.
ANSM can notify the applicant of its decision before the expiry of this 30 days deadline.
The chronology of evaluation is as follows:

- the conclusions of the first evaluation can be notified to the applicant in about 15 days;
- in the event of request for additional information, a response from the applicant is necessary within delay specified by ANSM (e.g. D22 if the conclusions of the first evaluation were returned within 15 days);
- and, in this case, the final decision of ANSM would be announced within 30 days.

Thus, for these trials, if the evaluation resulted in no objection or request for additional information, the final decision of ANSM could be formulated within 15 days and would then be notified by letter to the applicant.

Sometimes the applicant is not able to convey, within the time limits, the brief replies to the questions and requests formulated by ANSM.

If the applicant estimates that it will not be possible to convey the necessary elements within the delay specified by ANSM, the applicant then has faculty of withdrawing its request and of submitting it later on when the required elements become available (cf § 1.2.3.3 and 1.2.3.4).

1.2.3.3 Exchanges between ANSM and the applicant during the instruction of the file of request for AEC

1.2.3.3.1 Requests formulated by ANSM

Legislative and legal references
L.1123-8 article Article R. 1123-32 of the CSP

ANSM can:

- require from the applicant any additional information considered as necessary to decide concerning the request for authorisation;
- require that modifications are made to the research protocol;
- notify the applicant of its objections with their motivations to the implementation of research.

ANSM then fixes a delay for the applicant to address the required additional information, the modifications to its project, or its observations.

This delay does not suspend the one available to ANSM to make a decision concerning the request for authorisation.

1.2.3.3.2 Responses from the applicant

Responses must be submitted on working days.
There is no specific schedule for submitting responses to ANSM. These are examined without delay, from the day of their reception.

The applicant is able to convey part of responses, at distinct times, at the conditions to be in harmony with the time limit for responses specified by ANSM is.

If the applicant does not produce all of the elements requested within the time limit by ANSM, it is considered to have withdrawn its request.

If the applicant estimates that it will not be able to produce the elements requested within the time limit by ANSM, it can withdraw its request.

It is important to note that in the event of request for additional information from ANSM, the time limit for the applicant to provide this information starts at the date of receipt by the applicant of the letter from ANSM.

1.2.3.3.2.1 Response to requests for additional information or to motivate objections to the implementation of research formulated by ANSM

The methods of submission of the responses of the applicant are described in the form “Methods of sending dossiers”.

1.2.3.3.2.2 Transmission of a research protocol modified at the request of ANSM

A protocol modified at the request of ANSM is transmitted to the latter according to modalities of submission of responses described in the form “Ways of sending dossiers”.

Caution:

1. It is important to note here that insofar as the modification of the initial protocol of research is introduced at the initiative of ANSM (and not at the initiative of the applicant), the form of request for substantial modification (“Form of request for substantial modification”) is in no case to be used by the applicant to convey the modified research project.

Indeed, the use of this form is reserved for the submission of substantial modifications at the applicant’s initiative, after obtaining the AEC.

2. A modification of the research project introduced at the initiative of ANSM during the phase of evaluation of the request for AEC should not be conveyed to the concerned CPP for request of approval, but for information purposes only (cf § 1.3.1).

1.2.3.4 Withdrawal of the request for authorisation by the applicant

During the evaluation of its dossier of request for AEC by ANSM, the applicant has the chance of withdrawing his request when, for example, he is unable to produce elements requested within the time limit set by ANSM, in the event of a temporary cessation of research which has already begun in another country and for which the request for AEC is in the course of instruction at ANSM, or in the event of the trials not taking place in France.

In this case he informs ANSM as soon as possible, according to the methods described in the form " Ways of sending dossiers", while specifying, if necessary, the reasons for this withdrawal.

In addition, the withdrawal of a request for authorisation at ANSM does not imply the withdrawal of the request for notification lodged with a CPP.

1.2.3.5 New submission of a formerly withdrawn request

Following a withdrawal of request of AEC, the applicant can submit a new request later on. It then uses the same registration number as that initially allotted by ANSM for the trial, supplemented by a letter (A in the event of 1st resubmission, B in the event of the 2nd resubmission and so on) (cf form-indexes "Instructions relating to the use of the form of request for AEC").

1.2.3.6 Modifications made by the applicant before the beginning of research

Article L. 1123-9 of the CSP specifies "that after the beginning of research [corresponding to the date of inclusion of the first person in France, namely the date of signature of the form of the procedure of approval], any substantial modification of on the initiative of the sponsor must obtain a favourable opinion from the committee and authorisation from ANSM, before its implementation,".

The methods relating to the submission of requests for substantial modification and their processing by ANSM are detailed in part II (substantial modifications) of this notice for sponsors.

It follows from the preceding that before the beginning of research, and in particular for the period of examination of the application for AEC, no request for authorisation of substantial modification can be submitted.

However, several particular situations must be considered insofar as requests for modifications made to the initial file (taken at the initiative of the applicant), may be relevant for the risk-benefit analysis of the research and relate to "substantial" elements in terms of safety. These modifications might be the result of the observation of new facts or serious adverse effects.

1.2.3.6.1 request for modification submitted before obtaining AEC

Although it is not in the spirit of the texts that modifications can intervene in the course of instruction of a request, these requests, which must be relevant in terms of safety and be justified by the applicant, might be the subject of an instruction by ANSM.

However, depending on their nature and the time of their submission (compared to the date of beginning of instruction of the file of request for AEC), the possibility of their being processed at the same time as the request for AEC will be examined by ANSM on a case-by-case basis.

Indeed, when the modification is not substantial and does not distort the evaluation carried out beforehand, the request for modification carried out during the processing of the dossier can be integrated into the initial request and thus not lead to a prolongation of the evaluation period.
On the other hand, when the importance of the modification is such as the ongoing processing of the dossier is called into question, the period for evaluation of the request for authorisation is prolonged within the limit of the duration of evaluation of a request for substantial modification.
There are also cases in which this modification renders the initial request null and void and thus constitutes a new request for AEC.

ANSM will acknowledge receipt of such requests for modification and will specify in this case:

- on the one hand, if they are admissible or not;
- in addition; concerning the delay and processing methods:

-if they can be processed at the same time as the request of AEC and with the same delay;
-if the delay for evaluation of the initial request for AEC is prolonged (within the limit of the period of evaluation of a request for substantial modification, cf § 2.2.2.4.2.3.2);
-if the request for modification is such as it will be considered that a new dossier (integrating this modification) for request for AEC has been submitted. The delay for processing of the new dossier will then begin starting from the date of receipt of this modification

The methods of sending of these requests are specified in the form “Ways of sending dossiers”.

1.2.3.6.2 Request for modification submitted after obtaining AEC but before the beginning of research

ANSM will allow the sponsor to submit a request for substantial modification after obtaining the AEC and before the effective beginning of research.

These requests may be processed by ANSM in accordance with the methods described in part II (substantial modifications) of this notice for sponsors.

The methods of sending these requests are specified in the form “Ways of sending dossiers”.

1.2.4 Decision of ANSM

1.2.4.1 Authorisation of biomedical research

Legislative and legal references

Articles L. 1125-1 and L. 1125-3 of the CSP
Articles R. 1123-32, R. 1123-33 and R. 1125-7 of the CSP

1.2.4.1.1 Expressed Authorisation and implicit authorisation

1.2.4.1.1.1 Trials subjected to explicit authorisation

Research relating to DM incorporating products of human or animal origin, or in the manufacture of which such components intervene, must be authorised explicitly, i.e. receive a written decision from the General Director of ANSM in order to be implemented.
For such research, when the evaluation delay of ANSM comes to an end, no answer from ANSM means the authorisation for research has been refused.

1.2.4.1.1.2 Trials subjected to implicit authorisation

Other biomedical research relating to DM or DM-DIV is not subject to explicit authorisation but to implicit authorisation.

For this sort of research, when the evaluation delay of ANSM (30 or 60 days) comes to the end, no answer from ANSM means the authorisation for research has been agreed.

When ANSM requires additional information, and if the applicant conveys this in due time, the research is authorised implicitly if ANSM does not answer to the applicant when the evaluation period comes to the end.

For trials subject to implicit authorisation, the sponsor can ask ANSM, at the end of the legal period of 30 or 60 days, to deliver a certificate confirming that the research has been authorised by ANSM, in the case where ANSM has not notified its decision before the end of the 30 or 60 days period depending on the case.

1.2.4.1.2 Validity of the authorisation of a clinical trial

1.2.4.1.2.1 Period of validity

The authorisation of biomedical research delivered by ANSM applies to the whole period of the research, as provided for in the form of request for AEC (cf. form“Form of request for AEC/approval”).

This applies provided the trial begins within a one year deadline after delivery of the AEC and provided no modification and that no new element comes into play once the research is authorised, calling into question the AEC initially delivered by ANSM.

1.2.4.1.2.2 Request for information/suspension/ban

Pursuant to the provisions of article L. 1123-11 of the CSP, ANSM can at any time after the delivery of the AEC:

- solicit from the applicant additional information on the research;
- in the event of risk to public health or absence of response from the applicant or if ANSM estimates that the conditions, under which the research is performed do not any longer correspond to the conditions indicated in the request for AEC or do not respect the legislative and legal provisions:
  - to ask that modifications be made to the methods of carrying out the research, or to any document relating to the research;
  - to suspend or ban this research.

Except in the event of imminent risk, a modification to protocol at the request of ANSM or a decision of suspension or ban may only arise after the sponsor has been able to present his observations.

1.2.4.1.2.3 Nullity

The authorisation for biomedical research becomes null and void within one year following the date of its being granted if research has not begun in France within this time.

As a reminder, the beginning of research corresponds to the date of the signature of the assent by the first person who undertakes it in France. This effective date of the beginning of the trial must be declared to ANSM.

Thus, it is important to note that in the absence of declaration from ANSM of the date of beginning of research within one year following obtaining the AEC, the latter becomes null and void.

However, before expiry of the one year period, the applicant can request from ANSM the extension of the validity of the authorisation, on presentation of a justification. This request must be submitted within 2 months before the date of nullity of the AEC, in accordance with the methods described in the form “Ways of sending dossiers”.

1.2.4.1.3 Scope of authorisation

1.2.4.1.3 What the authorisation concerns

The authorisation granted authorises the implementation of biomedical research, provided a favourable decision has been delivered by a CPP.

1.2.4.1.3.2 What the authorisation does not concern

Certain of the following points must be the object of specific authorisations.

This list is not exhaustive.

1.2.4.1.3.2.1 Collections of biological samples

Legislative and legal references

Article L. 1123-12 and L. 1243-3 (as resulting from law n° 2004-800 of August 6, 2004 relating to bioethics) of the CSP

In the event of the constitution of a CEB solely for the needs of biomedical research, the collection is the object of a declaration in ANSM which must be enclosed with the dossier of request for AEC (cf. § 1.2.1.1.5.1). Although enclosed in the dossier of request for AEC, the collection thus notified to ANSM is not the object of an authorisation by ANSM.

However, at the end of biomedical research, if the CEB is used to scientific ends, the organisation which ensures the conservation of it must, beforehand, declare it to the minister in charge of research. If the organisation is an health establishment, the statement is then made jointly to the minister in charge of research and to the director of the relevant regional health authority.

The organisations responsible for the CEB then concomitantly submit their project of declaration for the approval of a CPP (cf. article R. 1123-21 of the CSP).

1.2.4.1.3.2.2 Biomedical authorisation of place of research

Legislative and legal references

Article L. 1121-13 of the CSP
Articles R. 1121-11 with R. 1121-16 of the CSP

The authorisation of the clinical trial does not authorise the place of research.

The place of research must be authorised when the trials are carried out:

- outside healthcare structures,
- in any hospital service or any other place of exercise of health professionals when this research:

requires acts other than those which they usually practiced within the framework of their activity;
or when this research is carried out on persons presenting a clinical condition distinct from that for which service is competent.

This authorisation is granted for a 5 year period by the representative of the State in the area concerned (Prefect) or by the Minister for defence, if the place comes under its authority.

A copy of the authorisation of place is provided by the applicant in the dossier of request for AEC.

1.2..4.1.3.2.3 Authorisations relating to radiopharmaceutical drugs

Legislative and legal references
Article L. 5121-1 of the CSP Article R. 1333-24 of the CSP

By radiopharmaceutical drug is understood any drug which, when it is ready for use, contains one or more radioactive isotopes, called radio nuclides, incorporated for medical use.

The use and the detention of radio nuclides, for their use in biomedical research, and products or devices containing them, are subject to authorisation by the minister in charge of health.

A copy of this authorisation, delivered by the Directorate-General of nuclear safety and protection against radiation (DGSNR), must be added to the dossier of request for AEC.

1.2.4.2 Refusal of authorisation of biomedical research and means of appeal

1.2.4.2.1 Methods of refusal

- For research subject to implicit authorisation (cf. § 1.2.4.1.1.2), the decision of a refusal of authorisation must be the object of a motivated letter from ANSM specifying its objections to the implementation of research. This letter is addressed to the applicant within the delay for evaluation at ANSM.

- For research subject to explicit authorisation (cf. §1.2.4.1.1.1):
  - -ANSM can address to the applicant a letter with justifications specifying the objections to the implementation of research before the expiry of the period of evaluation.;
  - -No response from ANSM within this period signifies the authorisation for research has been refused.

1.2.4.2.2.2 Means of appeal

The applicant has the possibility of appealing to the General Director of ANSM, or to a judge within the administrative court.

The details of implementation of these means of appeal and an enumeration of their processes, one compared with the other, are hereafter described.

1.2.4.2.2.1 Appeal to ANSM

In the event of a refusal of authorisation for research, the applicant can appeal the decision to the General Director of ANSM.

Any appeal to the General Director of ANSM formulated after the expiry of a two month deadline following notification of the decision makes it impossible for the sponsor lodge an admissible contentious appeal against the aforementioned decision.

1.2.4.2.2.2 Right of review (judicial)

If the applicant wishes to challenge the refusal for request for authorisation, a judicial appeal can be undertaken before a judge of administrative affairs within two months from the date of notification of the decision to the applicant, or from the date of notification of the decision resulting from appeal, as the case may be.

For research mentioned in article L.1125-3, it should be noted that in the event of implicit refusal of authorisation, the applicant can solicit ANSM, within the delay for the appeal (2 months), a declaration of the reasons for refusal. ANSM then has a one month deadline to communicate its reasons to the applicant. In this case, the time for appeal against the implicit decision of refusal of authorisation is extended to two months after the date the reasons for refusal are communicated to the applicant (cf. article 5 of the law n° 79-587 of July 11, 1979 relating to the reasons for administrative acts and the improvement of relations between the administration and the public).

1.3 Exchanges of information between ANSM and CPP concerning request for authorisation/approval of research

Legislative and legal references
Articles L. 1123-7 and L. 1123-8 of the CSP Articles R. 1123-24 and R. 1123-32 of the CSP Decrees AEC and CPP

1.3.1 During the period of evaluation of the request

During the evaluation of the request for authorisation for research or approval, ANSM and the CPPP are constantly in touch over matters such as complementary requests for information, objections to the implementation of research, and requests for modifications that each may demand to the applicant.

To this end, ANSM and the CPP both receive all copies of letters addressed to the applicant.

Nevertheless, these exchanges are only for information purposes. Indeed, a request for modification formulated by ANSM during the phase of evaluation is not the subject of an evaluation by the CPP concerned.

In the same way, when the CPP requires the applicant to make modifications to its research project, these modifications will be made known to ANSM but will not be evaluated by it.

Moreover, as soon as the applicant has the authorisation from ANSM and the approval of the CPP, he transmits to both, under free format (cf. forms “Ways of sending dossiers”), for information purposes, the final version of the protocol of research and the booklet for the investigator, in the case where modifications have been made to these documents at the request of either.

Consequently, at the end of the periods of evaluation of ANSM and the CPP, both will have the same version of the documents.

1.3.2 At the end of the period of evaluation of the request

1.3.2.1 Elements transmitted by the applicant

Insofar as the authorisation for research may be implicit, the legislation demands (cf article R. 1123-32 of the CSP) that the decision of ANSM be communicated to the CPP by the applicant.

1.3.2.2 Elements transmitted by ANSM

Any written decision of ANSM is transmitted as a copy for information to the CPPP:
- in the case of trials subject to an authorisation arrangement expressed;
- in the case of trials subject to implicit authorisation and for which ANSM notifies the applicant of its written decision.

Moreover, ANSM informs the CPP promptly of its decisions of banning and suspension of research.

1.3.2.3 Elements transmitted by the CPP

The CPP informs ANSM of any decision.

1.4 Declaration of the beginning of research

The applicant must inform ANSM of the effective date of beginning of the trial, which corresponds to the date of the signature of the assent by the first person who consents to the research in France.

This declaration is carried out according to methods described in the form "Ways of sending files".

Caution: The authorisation of biomedical research becomes null and void within one year following date of delivery if research has not begun in France within this time (cf §1.2.4.1.2.1).

Consequently, it is important to declare.
to ANSM the date of beginning of research.

2 Modifications to the trial

Legislative and regulatory references			
	Title summary	Complete title	Publication
RIGHT FRENCH	Law of August 9, 2004	Law n° 2004-806 of August 9, 2004, modified, relati ng to the policy of public health	August 11, 2004
	Decree of April 26, 2006	Decree n° 2006-477 of 26 April 2006 modifying the c hapter 1st title II of the book 1st of the first part of the code of the public health relating to biomedical research	April 27, 2006
	Decree substantial modification	Order 24 August 2006 laying down the methods of presentation and the contents of the request for substantial modification of biomedical research relating to a medical device or in vitro diagnostic medical device to the French Agency of Medical Safety of the products of health and the committee of public safety	September 9, 2006

2.1 Preamble

Legislative and legal references

Article L. 1123-9 of the CSP

According to the provisions of article L. 1123-9 of the code of the public health, after the beginning of research, any substantial modification to it at the initiative of the sponsor, must be authorised by approval from a CPP and an authorisation from the relevant authority before implementation.
However, other types of modifications not referred to in this article of law must be taken into account.

Thus, this chapter will deal with the various types of modifications likely to be made to research, namely:

1. substantial modifications concerned by the provisions of article L. 1123-9 of the CSP (cf. §2.2).

Two typologies of substantial modifications are presented:

- substantial modifications submitted for authorisation from ANSM (cf. §2.2.2);

-substantial modifications submitted for information purposes to ANSM (cf. §2.2.3).

2. other modifications not provided for in the article above (cf. §2.3) such as;

- modifications taken at the initiative of the applicant (cf. §2.3.1) but:
  - -which are not substantial,
  - -which are substantial and for which a request for authorisation was submitted to ANSM before the beginning of research,

- modifications introduced at the request of ANSM (cf. §2.3.2):
  - -for the period of evaluation of the request for AEC, in accordance with the provisions of article L. 1123-8 of the CSP,
  - -after delivery of the AEC, in accordance with the provisions of article L. 1123-11 of the CSP.

2.2 Substantial modifications at the initiative of the sponsor

2.2.1 Definition

Legislative and legal references

articles R.1123-35 to 37 of the CSP
Decree substantial Modification

In accordance with the provisions of article R. 1123-35 of the CSP, substantial modifications are those which have a significant impact on any aspect of research, in particular according to the following criteria:

- the protecting the public, in particular as regards safety,
- conditions of validity of the research,
- if necessary, the quality and safety of the products tested (DM or DM-DIV being the object of research and possibly other products used within the framework of research),
- the interpretation of the scientific documents accompanying the course of research (in particular protocol, the investigator's manual or the form of request for trial authorisation),
- how the research is managed.

Only substantial modifications are subjected to authorisation and/or approval. ANSM and the CPP come to a conclusion concerning substantial modifications made to the elements of the file which were initially submitted to them. The sponsor informs ANSM and the CPP of the substantial modifications made to the elements of the file which were not submitted to them beforehand as soon as the decision of ANSM is known.

Examples of substantial modifications are presented in the form "Examples of substantial modifications".

The criteria defined by the law as well as the examples given in the form "Examples of substantial modifications" must be regarded as a guide for the sponsor to whom, *in fine*, the responsibility of qualifying a modification as substantial or not depends on, taking into account all the elements in its possession.

2.2.2 Substantial modifications submitted for authorisation to ANSM

Legislative and legal references

Article R. 1123-35 of the CSP

Decree substantial Modification

At the moment of a request for substantial modification, ANSM does not examine and authorises only the aspects concerned with its competence and not those concerning competence of the CPPP (cf. form “Field of competence of ANSM”).

The aspects coming under the responsibility of ANSM can:

1. also come under the responsibility of the CPP

In this case, the sponsor must request at the same time a request for authorisation for substantial modification (AMS) to ANSM and a request for approval from the CP (e.g. modification of the criteria of inclusion or non inclusion).

2. not come under the responsibility of the CPP

In this case the promoter informs the CPP that modifications were made on such or such aspect of the trial as soon as the authorisation of ANSM was acquired.

It should be noted that aspects within the competence of the CPP are addressed for information to ANSM as soon as the approval of the CPP is notified.

2.2.2.1 Contents of the dossier of request for authorisation of substantial modification (AMS)

2.2.2.1.1 Contents

Legislative and legal references

Decree substantial Modification

The contents of the dossier of request for authorisation of substantial modification (AMS) are detailed in the form “Contents of the dossier of request for substantial modification”. It comprises:

1. letter of request for substantial modification;

2. the form of request for substantial modification (cf. “Form of request for substantial modification”);

   This form is available:
   - on the Internet site of ANSM www.ansm.sante.fr, headings “Clinical trials”/“medical devices and medical devices of in vitro diagnostic”)
   - or, by request from UVEC (cf. form “Contacts/dossier follow-up”);

3. information justifying the merit of the modification requested, including in particular, a summary of the new data, an updated evaluation on the benefit and risks of research and possible consequences for the persons already included in it, as well as for the interpretation of the research results ;

4. the modified version of the documents submitted at the time of the request for AEC, revealing explicitly in the text the modifications made and mentioning the date and the number of the new version of these documents;

5. a comparative table (if applicable) highlighting the substantial modifications made to the document(s)

NB:
The same request for AMS can concern:
- several modifications concerning the same research;
- or only one modification concerning several trials relating to the same device and carried out by the same sponsor;

Such situations must be specified in the letter of request for AMS (cf. Form “Contents of dossier of request for substantial modification”) and the form of request for AMS.

2.2.2.1.2 Language

The documents making up the dossier of request for AMS addressed to ANSM can be compiled in French or English, except those which must be written in French (cf § 1.2.1.2) of the chapter I “Beginning of the trial” of this notice for sponsors).

2.2.2.2 Methods of submission of the file to ANSM

2.2.2.2.1 Who submits the file?

The file of request for AMS is addressed to ANSM by the applicant who may be:

2. the sponsor,
3. or the legal representative of the sponsor,
4. or the person or organisation delegated by the sponsor or its legal representative for submitting the request.

The applicant who deposits a request for AMS can be the same as that which deposited the file of request for AEC.

If this is not the case, the change of applicant may be notified by the new applicant within the framework of a request for substantial modification submitted to ANSM and the CPP.

2.2.2.2.2 When does the instruction begin on the dossier?

The beginning of examination of the application corresponds to the date of receipt of the full dossier .

2.2.2.3 How should the dossier be submitted?

2.2.2.3.1 Depositing electronically

The dossier of request for AMS is submitted to ANSM electronically, according to the methods described in the form “Ways of sending files”.

2.2.2.3.2 Depositing by post or messenger

In exceptional circumstances, it is possible to transmit the file of request for AMS by post or messenger. In this case, the applicant must respect the methods described in the form "Ways of sending dossiers".

2.2.2.4 Instruction by ANSM of the dossier of request for authorisation of substantial modification

Legislative and legal references
Article R. 1123-36 of the CSP Decree substantial Modifications

The evaluation by ANSM of the dossier of request for AMS comprises:

- the examination of its completeness (criteria fro technical and legal admissibility),
- technical assessment.

The stages of examination of admissibility and technical assessment start at the same time - the date of the beginning of evaluation of the application (cf § 2.2.2.2.2).

Caution: The calculation of the days is done in calendar days, and thus includes working days as well as public holidays (Saturday, Sunday and public holidays).

It is possible to obtain information concerning the follow-up of the dossier of request for AMS submitted (cf. forms "Contacts/dossier follow-up").

2.2.2.4.1 Admissibility/Acknowledgment of reception

The evaluation of the admissibility of the dossier of request for AMS, the criteria of admissibility, the delay for evaluation of admissibility and the notification of the admissibility of the file are identical to those described for the dossier of request for AEC (cf. §.1.2.3.1 of part I "Beginning of the trial" of this notice for sponsors).

Caution: It is important to note that: - notices of receipt issued by the postal service; - notices of receipt delivered by messengers by any agent at reception of ANSM; - the notifications of reception of emails, generated automatically by electronic messengers, do not constitute acknowledgment of delivery and admissibility of the request for AMS within the meaning of article 19 of law n°2000-321 of April 12, 2000 relating to citizen's rights in their relationships to the administrations.

2.2.2.4.2 Evaluation of the dossiers by ANSM

2.2.2.4.2.1 Organisation

The dossier of request for AMS are processed in the same way as the the dossier of request for AEC (cf. § 1.2.3.2 of part I "Beginning of the trial" of this notice for sponsors).

2.2.2.4.2.2 Object of the evaluation

ANSM makes a decision, concerning substantial modifications relating to those aspects coming under its responsibility (cf. form “Field of competence of ANSM”).

2.2.2.4.2.3 Delay for evaluation

The beginning of the evaluation of a dossier of request for AMS is defined in the same way as for the dossier of request for AEC (cf. § 1.2.3.2.3.1 of part I “Beginning of the trial” of this notice for sponsors).

Caution: The calculation of days is done in calendar days and thus includes working days as well as public holidays (Saturday, Sunday and public holidays).

- The case of substantial modifications of research subject to implicit authorisation

The delay for processing of a request for AMS cannot exceed 35 days starting from date of reception of a complete dossier.

ANSM may notify the applicant of its decision before the expiry of this 35 day deadline.

As an indication, the processing of the dossier of request for substantial modification should be carried out according to the following chronology:

- the conclusions of the first evaluation made available to the applicants within 15 days,
- in the event of request for additional information, a response from the sponsor is necessary within a time limit determined by ANSM (e.g. 22 days if the conclusions of the first evaluation were returned in 15 days);
- and, in this case, the final decision of ANSM should intervene at the latest before 35 days.

Thus, if the evaluation has not given rise to a fundamental question halting the procedure, the final decision of ANSM may be formulated in 15 days and is then notified by letter or fax to the applicant.

- The case of substantial modifications of research subject to explicit authorisation

These are the trials mentioned in 4° of article R. 1125-7 of the CSP, namely:

- trials relating to a medical device incorporating products of human or animal or biological origin or in the manufacture of which such components come into play;

In the event of request for AMS concerning such research, no answer from ANSM at the end of the 35 day deadline starting from the date of reception of a dossier of request for AMS considered complete means authorisation of the modification has been refused.

2.2.2.4.2.4 Exchanges between ANSM and the applicant during instruction of the dossier

2.2.2.4.2.4.1 Requests formulated by ANSM

ANSM may:

- require from the applicant any additional information which it considers necessary to make a decision about the request for AMS;
- require that modifications are made, in particular concerning the elements provided within the framework of the request for AMS;
- notify the applicant of its justified objections to implementation of the substantial modification.

ANSM then fixes a time limit for the applicant to submit the required additional information, depending on the case, , its modified project or its arguments. This time limit does not postpone that available to ANSM to make a decision concerning the request for AMS.

2.2.2.4.2.4.2 Response of the applicant

The answers must be submitted on working days.

There is no fixed schedule for depositing responses. These are examined without delay, starting from their receipt.

The applicant can provide brief replies separately, at other times, subject to respecting the deadline for responses fixed by ANSM.

If the applicant does not produce the elements requested before the deadline, he is considered to have withdrawn his request for AMS.

It is important to note that in the event of a request for additional information from ANSM, the deadline to the applicant to provide this information starts from the date of receipt by the applicant of the letter or the fax from ANSM.

2.2.2.4.3 Decision of ANSM

2.2.2.4.3.1 Authorisation of substantial modification

Legislative and legal references

Article R. 1123-37, R.1125-8 of the CSP

The methods of decision of ANSM related to the of AMS depend on the type of authorisation to which research is subjected, namely implicit authorisation or explicit authorisation (cf. §1.2.4.1.1 of part I “Beginning of the trial” of this notice for sponsors).

The different methods of decision are described hereafter.

2.2.2.4.3.1.1 Substantial modification of research subjected to implicit authorisation

For research subjected to implicit authorisation, no answer from ANSM at the end of the evaluation period (35 days) signifies authorisation.

If ANSM estimates that the request for modification is not acceptable, it informs the applicant within a 15 day deadline from the date of reception of the request and determines a time limit in which the applicant may present his observations.

When ANSM requires additional information, and if the applicant provides this within the allotted time, the modification is authorised implicitly if ANSM does not answer the applicant before expiry of the period of evaluation.

The applicant can request from ANSM the delivery of a certificate specifying the date on which the modification was authorised implicitly. This request is formulated in the letter of request for AMS enclosed with the dossier.

2.2.2.4.3.1.2 Substantial modification of research subject to explicit authorisation

The substantial modifications of research subject to expressed authorisation must be authorised by written decision of the General Director of ANSM.

2.2.2.4.3.1.3 Clinical trials subject to explicit authorisation

These are the trials mentioned in the 4° of article R. 1125-7 of the CSP, namely:
trials relating to a DM containing a product of human or animal origin or during the manufacture of which such components enter into play;

In the event of request for AMS for research relating to a DM mentioned above, no answer from ANSM at the end of the 35 day deadline from the date of notification of the admissibility of the request of AMS means the authorisation is refused

2.2.2.4.3.2 Refusal of authorisation of substantial modification and means of appeal

The modalities of refusal of authorisation by ANSM and resort by the applicant are identical to those described for the request for AEC (cf. §.1.2.4.2 of part I "Beginning of the trial" of this notice for sponsors).

2.2.2.5 Particular cases

2.2.2.5.1 Temporary suspension of research

Legislative and legal references
article R.1123-55 Decree substantial Modification

The temporary suspension of a clinical trial may consist of:

- the ending of the inclusion of persons in the trial;
- and/or the ending of the use of DM or DM-DIV which is the object of research for all or part of the persons already included in the trial.

Any decision by the sponsor to suspend research temporarily must be dealt with by:

- firstly and immediately, informing ANSM and CPP concerned, preferably by email or fax;
- secondly and within a maximum of 15 days from the date of suspension, of a request for substantial modification concerning this temporary suspension addressed for authorisation to ANSM and for approval to the CPP concerned (cf. form "Contents of file of request for substantial modification").

2.2.2.5.2 Resumption of research after temporary suspension

Legislative and legal references

Decree substantial Modification

When the sponsor wishes to resume research that it has suspended, it must first of all obtain the authorisation of ANSM and the approval of the CPP concerned (cf. form "Contents of dossier of request for substantial modification").

Research can resume only after authorisation of ANSM and approval of the CPP.

2.2.2.5.3 Modifications consecutive to a new event / urgent safety measures

Legislative and legal references

Article L 1123-10 2nd subparagraph of the CSP
Article R. 1123-55 of the CSP

The occurrence of a new event may, in certain cases, result in the setting up by the sponsor of urgent safety measures in order to protect the participants against an immediate danger. The sponsor sets up these urgent measurements without waiting for the authorisation of ANSM.

If the occurrence of a new event results in the setting up by the sponsor of urgent safety measures and the modification of the research, including temporary suspension of the research (cf. § 2.2.2.5.2), the sponsor is required to:

- inform ANSM and the CPP immediately of these new events and measures taken, preferably by email or fax;
- address to ANSM a request for authorisation of substantial modification and approval from the CPP concerned within 15 days maximum from the implementation of urgent measures, (cf. form "Contained file of request for substantial modification").

If the occurrence of the new event leads to suspension of research, the sponsor is required to inform ANSM and the CPP immediately and to submit to them the declaration of the end of research according to methods described in part 4 "End of the trial" of this notice for sponsors.

2.2.3 Substantial modifications transmitted for information to ANSM

Legislative and legal references

Article R. 1123-35, R.1123-36 of the CSP
Decree substantial Modification

2.2.3.1 Modifications relating to aspects not under the responsibility of ANSM

Substantial modifications relating to aspects not under the responsibility of ANSM (cf. form "Scope of competence of ANSM"), but only of that of the CPP, are transmitted for information to ANSM after the CPP has given its opinion on these modifications.

The CPP informs ANSM of the decision taken on these substantial modifications (cf form "Contained substantial modification record").

2.2.4 Modifications made at the initiative of the sponsor

2.2.4.1 Other modifications: non substantial modifications

Nonsubstantial modifications are those which do not have significant impact on any aspect whatever of the research.

These modifications do not have to be transmitted to ANSM, for authorisation, or for information purposes.

They must nevertheless be documented. In the event of inspection, they must be made available to the sponsor and/or at the location of the research (for the modifications which relates to them).

Examples of non substantial modifications are presented in the form "Examples of substantial and non substantial modifications".

2.2.4.2 Modifications made before the beginning of research

These situations are described in § 1.2.3.6 of part I "Beginning of the trial" of this notice for sponsors.

2.2.5 Modifications made at the request of ANSM

The modifications required by ANSM do not concern the provisions of the article L 1123-9 of the CSP but of the provisions of the articles L 1123-8 and L 1123-11 of the CSP.

2.2.5.1 Modifications requested by ANSM for the period of evaluation of the request for AEC

Legislative and legal references

Article L 1123-8 of the CSP

Such modifications are discussed in § 1.2.3.3.1 of part I "Beginning of the trial" of this notice for sponsors.

2.2.5.2 Modifications after delivery of AEC

Legislative and legal references

Article L 1123-11 of the CSP
Article R. 1123-57 of the CSP

In accordance with the provisions of article L 1123-11 of the CSP, in the event of risk of public health or in the event of absence of response from the sponsor to a request from ANSM or if ANSM judges that the conditions under which research is implemented do not correspond any longer to the conditions indicated in the request for AEC or do not respect the legislative and legal provisions,

ANSM can at any time request that modifications be made to the methods of carrying out research and any document relating to the research (such as the research protocol for example).

Except for the case of imminent risk, the applicant then has a one week deadline to present his observations counting from either the reception of the request for modification of the protocol, or of the decision of suspension or ban.

Such modifications should not be the object of a request for AMS, but be transmitted to ANSM according to methods specified in the form "Ways of sending dossiers".

They should not be the subject of a request for approval from the CPP concerned, but be transmitted to it, for information, by the applicant.

3 Vigilance

Legislative and regulatory references			
	Title summary	Complete title	Publication
FRE	Law of August 9, 2004	Law N 2004-806 of August 9, 2004, modified, relating to the policy of public health	August 11, 2004
NCH	Decree of April 26, 2006	Decree N 2006-477 of 26 April 2006 modifying the 1st chapter title II of the 1st book of the first part of the code of the public health relating to biomedical research (regulations)	April 27, 2006
LAW	Decree E.I.	Order of August 2006 fixing the form, the contents and the methods of the declarations of adverse effects and new elements occurring during biomedical research on a DM or DM-DIV	August 26, 2006
	Decree RAS	Decree of 16 August 2006 laying down the methods of declaration, the form and the contents of the safety report of biomedical research relating to a DM or DM-DIV	September 9, 2006

3.1 Introduction

This section provides recommendations on the collection, the checking, and the presentation of declarations of undesirable events/effects occurring during clinical trials of DM or DM-DIV, as well as the procedure for unblinding. Moreover, it specifies the responsibilities for each part concerned.

3.2 Scope of application

These recommendations apply to all the interventional clinical trials carried out on DM or DM-DIV in France.

3.3 Definitions

The definitions of article R. 1123-39 of the CSP apply. They are repeated in the form "Definitions and comments on definitions".

3.4 Responsibilities of the investigator

Legislative and legal references

Article R. 1123-54 of the CSP
Decree E.I. and FN (article 2)

The investigator notifies the sponsor, as soon as it becomes apparent, of all the serious undesirable events, except for those which are listed in the protocol or the booklet for the investigator as not requiring an immediate notification.

This initial notification is the object of a written report and is followed quickly by additional detailed report(s) The initial report and the follow-up reports must identify the participants in the trial by a unique code number to each of them so that this data is anonymous.

The undesirable events and/or the abnormal analysis results, defined in the protocol as determining elements for the evaluation of the safety of participants in biomedical research, are notified to the sponsor by the investigator, in accordance with the methods and checks specified in the protocol.

The investigator communicates additional information to the sponsor concerning serious undesirable events.

3.5 Responsibilities of the sponsor

3.5.1 General remarks

The sponsor is responsible for the continuous evaluation of safety of the DM or DM-DIV which are the object of research.
Is responsible for speedy notification to the investigators concerned, the CPP concerned and ANSM (as to the proper authorities and ethics' committees of the other Member States concerned in the European Community, if necessary), of any data which could affect the safety of the participants, have an impact on the of the trial on going or modify the AEC delivered by the proper authority for performing of trial.

3.5.2 Collection and evaluation of undesirable events

Legislative and legal references

Decree EI (articles 1 to 3)

The management of these cases comprises the evaluation of the data, the identification of the individual cases requiring care, the detection and the management of alerts and any other element resulting from the aggregate data.

Each undesirable event must be evaluated by the investigator and the sponsor, which includes the evaluation of the gravity and the causality between the undesirable event and the DM or DM-DIV or

the procedure of implementation of the DM which is the object of research or the associated treatment.(s).

In addition, the sponsor has to evaluate the unexpected or expected characteristics of the adverse effect.

The sponsor is required to maintain detailed registers of all the undesirable events which are reported to him by the investigators. These registers are to be transmitted to ANSM, at its request.

3.5.2.1 Evaluation of seriousness

Seriousness is defined in accordance with the definition of article R. 1123-39 of the CSP by taking into account the comments presented in the forms "Definitions and comments on definitions".

3.5.2.2 Evaluation of causality

Between the undesirable event and the DM or DM-DIV or the procedure of implementation of the DM which is the object of research or the associated treatment.(s).

Causality with the DM or DM-DIV must be determined in accordance with the definition of an adverse effect indicated in article R. 1123-39 of the CSP.

All the undesirable events for which the investigator or the sponsor estimates that a relation of causality exists with the implementation of the DM or DM-DIV which is the object of research must be regarded as potential causes of adverse effects.

All undesirable events for which the investigator or the sponsor estimates that a relation of causality with the procedure of implementation of the DM which is the object of research can be reasonably supposed are to be notified to ANSM and the CPP.

When the evaluations of causality carried out by the investigator and the sponsor differ, they must both be mentioned in the declaration addressed to ANSM. The evaluation carried out by the investigator must not be modified by the sponsor.

3.5.2.3 Evaluation of unexpected characteristics by the sponsor

It is advisable to use the definition of the term "unexpected adverse effect" which is given in article R. 1123-39 of the CSP, taking into account the comments presented in the form "Definitions and comments on definitions".

An adverse effect must be regarded as unexpected on the basis of the reference document, which is:

- the instruction notice or instructions for use, supplemented by the list of expected adverse effects and justification for the characteristics of these effects, when the device subject has an EC marking .
- the protocol or the booklet for the investigator, if this is not the case.

The reference document is identified clearly in the dossier for request for AEC at ANSM. This document can be compiled in French or English.

An adverse effect is regarded as unexpected if its nature, its severity or its evolution does not correspond with information available in the reference document for the DM or DM-DIV which the object of the research.

An expected adverse effect corresponds to an effect which has already been observed, it is not a potential risk for which there is no existing patient observation data and it is not an adverse effect whose usual frequency of occurrence is unknown.

3.5.2.4 Protection of personal data of participants in the trial

Data protection must be undertaken in conformity with law N 78-17 of January 6, 1978 (modified) relating to data processing, data files and liberties..

3.5.3 Declaration of safety data

The sponsor declares the safety data to ANSM starting from the date of authorisation of research in France.

It also declares to ANSM new elements which could have occurred during the period of evaluation of the request for AEC, as well as the annual safety report (RAS) if this is relevant.

3.5.3.1 Methods of declaration

3.5.3.1.1 What has to be immediately declared to ANSM?

Legislative and legal references

Article R. 1123-48 of the CSP
Decree EI and FN (articles 4 and 8)

A summary table of the safety data to be declared to ANSM and the CPP concerned is available in the form "Diagram of declaration of safety data to ANSM and the CPP".

3.5.3.1.1.1 Suspicions of unexpected serious adverse effects (EIGI) and serious undesirable events likely to be related to the procedure of implementation of the DM which is the object of research

The sponsor declares to ANSM:

1. all suspicions of serious unexpected adverse effects due to a DM or DM-DIV which is the object of research;

2. all serious undesirable events likely to be related to the procedure of implementation of the medical device which is the object of research.

3.5.3.1.1.2 Other safety data requiring an immediate declaration

This is any safety data or any new element which could significantly modify the evaluation of the benefit to risk ratio of a DM or DM-DIV which is the object of the research, of the trial or which could

result in having to consider modifications concerning the use of the DM or DM-DIV which is the object of research or the trial methods, such as for example:

a) any clinically significant increase in the frequency of occurrence of a serious expected adverse effect;
b) suspicions of EIGI which have occurred with participants having finished the trial and who are notified by the investigator to the sponsor, as well as possible follow-up reports;
c) any new element concerning the clinical trial schedule or the use of the DM or DM-DIV, when this new element is likely to endanger the safety of the participants. As an example:
   - a serious undesirable event likely to be linked to the investigations and the procedures of diagnostic of the trial and which could modify the course of the trial,
   - a significant risk for the participants in the trial such as for example a lack of effectiveness of the DM or DM-DIV used in the treatment of a life threatening disease,
   - significant results resulting from a finished pre-clinical study which could call in question the evaluation of risks compared to expected benefit (such as a biomechanical study),
   - the anticipated stopping or a temporary interruption of a trial for reasons of safety carried out with the same DM or DM-DIV in another country,
   - an EIGI related to a non experimental health product necessary to the implementation of the trial (e.g. "challenge agents", emergency treatment);
d) recommendations of the independent inspection committee (DMC or DSMB), if necessary, if they are relevant to public safety;
e) any EIGI transmitted to the sponsor by another sponsor of another clinical trial involving the same DM or DM-DIV in another country.

3.5.3.1.2 What should not be declared immediately?

The following do not usually require an immediate declaration:

- expected serious adverse effects;
- non serious adverse effects;
- adverse events which are regarded as non related to the DM or DM-DIV which is the object of research or not related to the procedure of implementation of the DM which is the object of research.

3.5.3.1.3 Who must declare and to whom?

Legislative and legal references

Article L 1123-10 of the CSP
Articles R. 1123-45 and R. 1123-48 of the CSP
Decree EI and FN (article 4)

The sponsor must declare any of the information relating to safety described above to ANSM.

Thafety data to be transmitted to the CPP concerned are specified in § 3.5.3.1.6.5.

The sponsor must also submit to all the investigators concerned any information which may affect participants in the trial, in particular any relevant information relating to suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM which could have an unfavourable impact on participants' safety (cf. § 3.5.1).

3.5.3.1.4 Management of suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM associated with a comparator or a placebo

The sponsor must declare to ANSM and the CPP concerned any suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM related to the comparator even if the product benefits from an EC marking.

In all the cases, the declaration of suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM to ANSM and the CPP concerned is made only by the sponsor.

The events related to a placebo do not usually meet the criteria of a serious adverse effect and consequently do not require an immediate declaration. However, if suspicions of EIGI or undesirable events likely to be related to the procedure of implementation of the DM are associated with the placebo, in this case it is the sponsor's responsibility to declare them.

3.5.3.1.5 When should a declaration be made?

Legislative and legal references

Article R. 1123-48 of the CSP

3.5.3.1.5.1 Suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the fatal DM or threatening immediate vital prognosis

ANSM and the CPP concerned must be informed without delay, and at the latest within 7 calendar days, starting from the moment the sponsor is informed for the first time of the minimum criteria permitting an immediate declaration of the EIGI or serious adverse events likely to be related to the procedure of implementation of the DM (cf § 3.5.3.1.6.1 min. criteria for the declaration of an EIGI or adverse events likely to be related to the procedure of implementation of the DM).

In all cases, relevant additional information must be sought and a follow-up report must be completed as soon as possible. This report must be transmitted to ANSM and the CPP concerned, within a new 8 day time limit from the 7 day deadline.

3.5.3.1.5.2 Other suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM

The other cases of EIGI or serious adverse events likely to be related to the procedure of implementation of the DM and the new safety elements described in § 3.5.1.1.2, must be declared to ANSM and the CPP concerned as soon as possible and at the latest in 15 calendar days starting from the moment when the sponsor is informed for the first time of the minimum criteria permitting the immediate declaration of the EIGI (cf. §3.5.3.1.6.1 min criteria for the declaration of an EIGI and undesirable events likely to be related to the procedure of implementation of the DM).

Relevant additional information must be transmitted, within a new 8 day time limit, starting from the 15 day deadline.

3.5.3.1.6 How should the declaration be made?

Legislative and legal references

Decree EI and FN (article 5)

3.5.3.1.6.1 Minimum criteria for the immediate initial declaration of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM

Obtaining complete information relating to the description and the evaluation of an adverse effect may not be possible within the time limit assigned for the initial declaration.

The initial declarations must be carried out as soon as the following criteria, defining a validated case, are known:

a) a DM or DM-DIV which is the object of suspected research or a procedure of implementation of the suspected DM;

b) an identifiable participant (for example by research identification code number);
c) an serious unexpected adverse event for which the link to the DM or DM-DIV which is the object of research or to the mode of implementation of the DM can be reasonably supposed by the investigator or the sponsor;
d) a notifier or an identifiable informant (investigator or another source);
e) obligatory administrative information, in particular a single identifier of the case (for example, the identification number of the case in the data base of the sponsor), if applicable;
f) the registration number of the trial obtained from ANSM.

3.5.3.1.6.2 Follow-up reports of suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM

In the event of incomplete information at the time of the initial declaration, all information permitting an adequate analysis of a link of causality must be sought from the notifier or other sources available.

The sponsor must declare all the additional relevant information, in the form of follow-up reports referenced and numbered according to same methods as the initial report.

In certain cases, it may be necessary to ensure a follow-up of the long-term evolution of a particular adverse effect e.g. effect having a potentiality of chronicity or after-effects or effects on the descendents).

3.5.3.1.6.3 Methods of declaring suspicions of EIGI or serious adverse events likely to be related to the procedure of implementation of the DM

Legislative and legal references

Decree EI and FN

The declaration is made electronically to ANSM.
If electronic transmission is somehow impossible; the sponsor addresses it by post,

.

However, whichever format (electronic or paper) used, it is important that the information described at the section 3.5.3.1.6.1is included in any immediate reporting (according to circumstances, some items may not be relevant).

3.5.3.1.6.4 Form and format of the reports for the other safety data which is the subject of an immediate declaration

Legislative and legal references

Decree EI and FN (article 8)

The new safety elements leading to an immediate declaration (cf. § 3.5.3.1.1.2) are addressed:
- to ANSM, electronically or exceptionally by post;
- to the CPP concerned, by post.

The declaration of a new element should include in particular the following information:
1. the registration number of the biomedical research,
2. the title of the biomedical research,

3. the code number of the protocol allotted by the sponsor,
4. a summary of the new element and suitable urgent measures of safety taken by the sponsor in this case,
5. any relevant information for the evaluation of the new element.

3.5.3.1.6.5 Declaration to the CPP

Legislative and legal references

Articles R. 1123-42, R. 1123-43 and R. 1123-47 of the CSP
Decree EI and FN (articles 5, 7 and 9)

The sponsor transmits to the CPP concerned:

- immediately and within the deadlines set out in §3.5.3.1.5:
  - suspicions of EIGI and the serious adverse events likely to be related to the procedure of implementation of the DM which have occurred in France in the trial concerned;
  - any new element or any new event which could have an unfavourable impact on participants' safety or on the method of trial (cf. § 3.5.3.1.1.2).

- semi-annually: a list of suspicious of EIGI and undesirable events likely to be related to the procedure of implementation of the DM which have occurred outside national territory in the trial concerned as well as those which have occurred in any other research that the sponsor is carrying out in France.
  This list is accompanied by a concise synthesis prepared by the sponsor putting forward the principal problems of safety raised.
  A copy of this declaration is addressed simultaneously to ANSM.

The sponsor communicates all further information requested by the CPP concerned on notified cases of death.

A summary table of safety data to be declared to the CPP concerned is available in the form "Diagram of declaration of safety data to ANSM and the CPP".

3.5.3.1.7 Identification of suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM - management of follow-up reports and doublon.

Legislative and legal references

Decree EI and FN (article 4)

The initial and follow-up reports of suspicions of EIGI and serious adverse events likely to be related to the procedure of implementation of the DM, must contain sufficient information to enable the identification of doublets. Doublets contain the repetition of the declaration of the same case (concerning the same patient, at the same moment of occurrence, for the same object).In particular the identifying code of the participant in the trial who presented this adverse effect must be unique for the same clinical trial, whatever the number of EIGI of undesirable events likely to be related to the procedure of implementation of the DM presented and the moment when they occurred.

When the sponsor identifies the presence of a doublet, it must inform ANSM and the CPP concerned.

3.5.3.1.8 Management of the adverse effects in clinical trials with blinded products.

Legislative and legal references

Decree EI and FN (article 7)

In general, the trial must be unblinded by the sponsor before the declaration of the EIGI and serious adverse events likely to be related to the procedure of implementation of the DM to ANSM and the CPP concerned.

Although it is useful to maintain the blind for all the participants before final analysis of the trial, when a serious undesirable event has to be declared, if safety measures are to be considered and informing the treatment group is necessary, the blind is lifted by the sponsor only for the subject having presented the undesirable event, even if the investigator has not done this.It is recommended, when possible and suitable, to maintain blinding for the people responsible for data analysis for the or the interpretation of the final results of the trial, such as the biometrics personnel.

The unblinding of individual cases by the investigator must be done only if this information may modify in some way the care provided to the patient.

Three situations resulting from unblinding are then possible:

a) if the DM used is the object of the trial: the case has to be declared immediately as a suspicion of EIGI,
b) if the DM used is the comparator: the unexpected character of the adverse effect will have to be evaluated by comparing it with reference document identified in the protocol. In the event of unexpected effect, the case has then to be declared immediately. In the opposite case, the event concerns an expected EIG not subject to immediate declaration,
c) if the product is a placebo: events related to a placebo do not usually meet the criteria for a serious adverse effect and consequently do not require an immediate declaration. However, if suspicions of EIGI are associated with the placebo, it is up to the sponsor to declare them.

3.5.3.1.9 Management of serious adverse effects in morbi-mortality trials

In exceptional cases, for morbi-mortality trials, when the principal criterion of evaluation defined in the trial protocol is mortality or another serious event in connection with the pathology, after agreement of ANSM requested by the sponsor at the time of the request for authorisation of clinical trial, the modalities of declaration of suspicions of serious effects or undesirable events can be modified. These modalities are then precisely defined in the research protocol (or in a document enclosed with it).

For these studies, the sponsor has to set up an inspection committee which is independent from the data. This committee is charged with examining safety data, in a regular way and when necessary, during the carrying out of the trial and making recommendations to the sponsor as for the continuation, the modification or the ending of the trial. Its composition and its functioning are described in the protocol.

When the opinion of this independent committee and its recommendations follows the description of data likely to call into question the safety of the participants, this data must be notified as quickly as possible by the sponsor to ANSM and the CPP concerned.

ANSM can require access to the decisions or recommendations of the independent inspection committee, as well as to any elements which the committee used to make any decision or to make any recommendation.

However, in these same studies, suspicions of EIGI or serious adverse events likely to be related to the procedure of implementation of the DM which are not effectiveness criteria must be declared in the normal way.

3.5.3.2 Annual safety reports

Legislative and legal references

Article R. 1123-53 of the CSP
RAS decree

3.5.3.2.1 Introduction

In addition to immediate declarations (and semi-annual), the sponsors of research establish a safety report relating to the clinical trial concerned once per annum, throughout the whole biomedical research or on request,.

This annual safety report of (RAS) is addressed:
- to ANSM, electronically or exceptionally by post;
- to the CPP, by post.

Its objective is to describe in a concise manner any safety information available for the clinical trial concerned and to evaluate the participants' safety.

3.5.3.2.2 Contents of the annual safety report of the clinical trial concerned

3.5.3.2.2.1 General case

The RAS of the trial includes three parts:

Part 1: Analysis of participants' safety;
Part 2: List of all suspicions of serious adverse effects (including EIGI) and list of serious adverse events which have occurred in the trial concerned in France and abroad, for the period covered by the report.
Part 3: Summary tables of all the serious adverse effects which have occurred in the trial concerned.

Part 1: Analysis of participants' safety

Here the sponsor provides a concise description of all the known relevant data it is aware of, which could have a significant impact on the population concerned and the report of the benefit to risks ratio of the trial.

Part 2: List of all suspicions of serious adverse effects and the list of serious adverse events being able to be related to the act of implementation of the DM, which have occurred in the trial

is a specific trial list of all suspicions of serious adverse effects and serious adverse events likely to result from the procedure of implementation of the DM which have occurred and been reported, during the trial, in France or outside national territory (including in intermediary countries) for the period covered by the report.

The list has to be identified by a reference number allotted by the sponsor or the printing date and hour, and must include the information described in the form "Contents of lists of serious adverse effects (part 2 of the annual safety report)".

This list shows the principal information but not necessarily all the details usually collected in individual cases.

Suspicions of EIG are organised according to a classification regrouping them by system or by organ.

Each participant should be mentioned only once, whatever the number of adverse effects reported for each case. If there is more than one effect, they must all be mentioned, but it is the most serious adverse effect (sign, symptom or diagnostic), as evaluated by the sponsor, which should appear first.
It can happen that the same participant presents several effects or undesirable events at different times. Such effects or events must be the subject of separate reports. In this case, the same subject would then appear more than once in the list, in which it would be necessary to indicate the link with the other effects.

Part 3: Tables of synthesis

In addition to the lists of individual cases (provided in part 2 of the RAS), it is necessary to include tables of synthesis including all the signs, symptoms or diagnoses of the serious adverse effects which have occurred since the beginning of research, permitting a overall picture of the trial.

They usually contain more terms than participants in the trial.

When the number of cases is very small, a narrative description may be more suitable.

The table of synthesis, must specify the number of cases listed:- for each class physiological system or organ concerned;

- for each kind of effect or undesirable event, by specifying its expected or unexpected character;
- for each treatment group of, after unblinding. If there are several treatment groups, the number of cases is specified for the DM or DM-DIV which is the object of research; the comparator or the placebo;
- if necessary, for treatment managed under blinding.

3.5.3.2.3 Delay for transmission of the annual safety report

The time limit for transmission of the annual safety report is calculated starting from the date of the beginning of the trial in the European Community.

The anniversary of this date is regarded as the deadline for including data in the report (closing date).The sponsor transmits the annual report within the 60 days following closing date, or on request.

When biomedical research concerned is of short duration, the RAS is transmitted within 90 days after the end of research, at the same time as the declaration of the end of the trial mentioned in article R. 1123-59 of the CSP [cf chapter 4 (End of the trial) of this notice for sponsors].

How should the investigators be informed?

Legislative and legal references

Article R. 1123-45 of the CSP

The sponsor informs all the investigators concerned of any data that could have an unfavourable impact on the participants' safety.

If appropriate, information can be gathered and presented in the form of a list of suspicions of EIGI and undesirable events likely to be related to the procedure of implementation of the DM, following a periodicity adapted to the nature of the project in development and the number of cases of suspicions of EIGI and undesirable events likely to be related to the procedure of implementation of the DM. This list must be accompanied by a summary of the updated safety profile of the DM or DM-DIV which is the object of research.

In the case of, a clinical trial with blinded products the list must present the data of all suspicions of EIGI, whatever the DM or DM-DIV used. Thus, if possible and applicable, the blinding has to be maintained, making it possible to avoid revealing information to the investigators concerning the identification of the DM or DM-DIV.

In the case of a significant event occurring related to safety, either after reception of an individual report, or after examination of the total data available, the sponsor must inform all the investigators as soon as possible.

A safety problem which has an impact on the carrying out of the clinical trial or the development project, including the suspension of the study programme or the decision to modify the protocol for safety reasons, must also be reported to the investigators.

3.5.5 Declaration of safety data after the end of the trial in the European Community

Legislative and legal references

Article R. 1123-60 of the CSP

After the end of the trial, any unexpected safety problem of which modifies the analysis of the benefit to risks ratio and which has an impact on the participants, must be reported to ANSM along with actions to be undertaken.

3.6 Role of ANSM

Legislative and legal references

Article L 1123-11 of the CSP

Article R. 1123-41 of the CSP

The law specifies that:

- ANSM can, at any time, require additional information on research from the sponsor;
- in the event of a risk to public health or in the event of absence of response from the sponsor or if ANSM judges that the conditions under which research is implemented do not correspond any longer to the conditions indicated in the request for authorisation of the clinical trial or do not respect the provisions relating to biomedical research, it can at any time demand that modifications be made to the methods of realisation of the research, or to any document relating to research, or suspend or prohibit the research.

The decree specifies that ANSM is to implement the vigilance system of related to clinical trials. It takes, if necessary, suitable steps to ensure public safety. It makes sure that all suspicions of EIGI and undesirable events likely to be related to the procedure of implementation of the DM which have occurred in France and brought to its knowledge are recorded. It is in contact with the proper authorities of the other Member States.

3.7 Role of CPP

The law (article L 1123-10) specifies that the CPP is to make sure, when necessary, that participants are informed of the E.I. which are declared to it, and that they confirm their assent.

The CPP can require additional information in the event of death of a participant.

4 End of the trial

Legislative and regulatory references			
	Title summary	Complete title	Publication
FRENCH LAW	Law of August 9, 2004	Law N° 2004-806 of August 9, 2004, modified, relating to policy of public health (Article L 1123-11 of the CSP)	August 11, 2004
	Decree of April 26, 2006	Decree N 2006-477 of 26 April 2006 modifying the 1st chapter title II of the 1st book of the first part of the code of public health relating to biomedical research (regulations) - (Article R. 1123-59 of the CSP)	April 27, 2006
	End of trial	Order of August 2006 relating to the contents and the methods of presentation of information relating at the end of research, the final report and the summary of the final report of a biomedical research relating to a DM or DM-DIV	September 9, 2006

The end of the trial is declared to ANSM, according to the methods detailed hereafter, by:

- the sponsor,
- or the legal representative of the sponsor,
- or the person or organisation charged by the sponsor or his legal representative to submit the request for AEC.

This chapter only deals with the definitive ends of trials and not with temporary interruptions whose declaration in ANSM is subjugated to methods defined in chapter II (substantial modifications) of this notice for sponsors (§ 2.2.2.4.4.1 and § 2.2.2.4.4.2).

4.1 Definition of the end of the trial

Generally, the end of the trial corresponds to the date of the last visit of the last participant.

Any other definition of the end of the trial attributed by the sponsor must be specified in the trial protocol.

In the course of the trial, any modification to this definition must be the object of a request for substantial modification to research, according to the methods specified in part II (substantial modifications) of this notice for sponsors.

4.2 When must the end of the trial be declared?

The sponsor declares the end of the trial in two types of situations to ANSM:

- when research reaches its predetermined end (on-time end);
- when research is stopped in some premature manner (premature end).

4.2.1 In the event of the end of trial at on-time end

The sponsor draws up a declaration of end of trial within 90 days following the end of research:

- when the research is finished in France,
- and also when, if the research is multinational, when it is finished in all of the countries where it is carried out, whether these countries be located inside or outside the European Community.

For the same research undertaken in several countries, the sponsor may have to address two declarations of end of research to ANSM, if the research does not come to an end simultaneously in France and in all the other countries concerned.

4.2.2 In the event of premature end of the trial

If biomedical research is stopped (definitively) prematurely, the sponsor declares this within 15 days and indicates the reasons justifying it.

As an example, a research must be the object of a declaration of premature end in the following situations:

- research does not begin in spite of obtaining authorisation from ANSM and approval from a CPP;
- research is definitively stopped by the sponsor after being temporarily stopped;
- research is suspended by ANSM.

For memory [cf. chapter 2 (substantial modifications) of the notice for sponsors § 2.2.2.5.1:in the event of temporary interruption of biomedical research, the sponsor must immediately inform ANSM and address a request for substantial modification notifying this temporary interruption , within the 15

days following the date of this interruption. If, later on, this temporary interruption proves to be definitive, the sponsor should then address a declaration of premature end of trial to ANSM.

4.3 How must the end of the trial be declared?

4.3.1 Contents of the dossier of declaration of end of trial.

The sponsor addresses to ANSM a dossier comprising the following two elements:

- a letter specifying :
  the registration number of the trial allotted by ANSM;
  the total number persons included in the research in France;
- the form of declaration of end of trial available on the Internet site of ANSM (cf. form "Form of declaration of end of trial").

4.3.2 Methods of submission of the dossier of declaration of end of trial.

The dossier must be submitted to ANSM according to methods described in the form "Ways of sending dossiers".

4.4 Particular case:ending of a trial begun in a country other than France and for which the request for AEC is in the course of instruction at ANSM

An international trial may have begun in another Member State from the European Community that in France or in an intermediary country while the request for authorisation of this trial is in the course of instruction at ANSM.

If, for whatever the reason, the trial carried out in this other country is stopped prematurely, its sponsor is asked to:

- not address a declaration of end of trial;
- but, if it does not wish to carry out the trial in France, to specify to ANSM that it withdraws its request for AEC in accordance with the methods of withdrawal of such a request detailed in § 1.2.3.3 of the chapter I "beginning of the trial" of this notice for sponsors.

5 Trial results

Legislative and regulatory references			
	Title summary	Complete title	Publication
FRENC	Decree of April 26, 2006	Decree N° 2006-477 of 26 April 2006 modifying the 1st chapter title II of the 1st book of the first part of the code of public health relating to biomedical research (regulations) - (Article R. 1123-60 of the CSP)	April 27, 2006
	Order End / Final report	Decree of 25 August 2006 relating to the contents and the methods of presentation of information relating at the end of research, the final report and the summary of the final report of biomedical research relating to a DM or DM-DIV	September 09, 2006

H L A W	Decree Repertory		To appear

5.1 Trial results:final report and summary of the final report

The sponsor draws up a final research report as well as a summary of this final report.

5.1.1 Final report

The plan of the final report is detailed in the FORM "Plan of the final report ".

The final report is to be drawn up within one year following the end of the trial in all of the countries where research was undertaken (on-time or premature end).It is not addressed to ANSM but is held at its disposal.

5.1.2 Summary of the final report

The summary of the final report is presented according to the format available on the Internet site of ANSM or in paper version at request to ANSM. The contents of the summary of the final report are detailed in the form "summary of final report ".The information which must appear in it is that which relates to the whole of the trial, and not only that referring to France.

- Methods of sending the summary of the final report

The summary of the final report is established within one year following the end of research in all of the countries where research was undertaken It is addressed to ANSM electronically. If this means of sending is not possible, the sponsor addresses, by letter, the summary of the final report.

6.Repertory of authorised clinical trials

Legislative and regulatory references			
	Title summary	Complete title	Publication
FRENCH LAW	Law of August 9, 2004	Law N° 2004-806 of August 9, 2004, modified, relati ng to policy of public health (article L 1121-15 of the CSP)	OJ of August 11, 2004
	Decree of April 26, 2006	Decree N° 2006- 477 of 26 April 2006 modifying the 1st chapter title II of the 1st book of the first part of the code of public health relating to biomedical research (regulations) (article R. 1121-17 of the CSP)	OJ of April 27, 2006
	Decree Repertory		To appear
	Decree AEC	of August 2006 fixing the contents, the format and the methods of presentation at the French Agency of Medical Safety of the products of health of the dossier of request for authorisation for biomedical research relating to a medical device or in vitro diagnostic medical device	OJ of April 26, 2006
	Order End/Final report	Decree of 24 August 2006 relating to the contents and the methods of presentation of information relating at the end of research, the final report and the summary of the final report of biomedical research relating to a medical device or in vitro diagnostic medical device	OJ of September 9 2006

After publication and implementation of the decree fixing the contents of the repertory of authorised clinical trials relating to medical devices or medical devices of in vitro diagnostic, ANSM will set up and will publish this repertory.

By authorised research is understood ECs:

- authorised by ANSM,
- and which obtained approval from a CPP.

This repertory will be freely accessible on the Internet site from ANSM at the following address: < http://www.ansm.sante.fr >.

The sponsor of a research will be able to oppose, for legitimate reasons, its publication in the repertory. The methods of instruction by ANSM to the opposition of the sponsor will be specified in the form "Repertory of authorised biomedical research".

Lastly, the type of research as well as information regarding it which may be published in the repertory will also be specified in the form "Repertory of authorised biomedical research".