

# Clinical trials on medicinal products submitted to the ANSM as part of the Fast- Track procedure

Practical Information Guide for Applicants  
*Test phase - October 2018*

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## I. INTRODUCTION

Making health innovation accessible faster for patients is a priority that the government has posted in the CSIS 2018 (Strategic Council of Health Industries) and that the ANSM, guarantor of the safety and quality of the authorizations issued, integrated into its 2018 work program.

Two fast-track programmes are planned within the context of the ANSM's priority projects, focussed on access to innovation and support for development respectively.

This procedure aims to reduce clinical trial authorisation application processing times, to prepare the ANSM to be more responsive in provision of the future European regulations on clinical trials, and to improve the quality and safety of the submitted applications.

The main challenge in setting up this Fast-Track procedure for medicinal product clinical trials is to enable more rapid access to:

- innovative treatments for patients ("Access to innovation" => Fast-Track 1)
- implementation of new clinical trials on known substances ("Support for development" => Fast-Track 2)

A first phase of this test procedure will be proposed to volunteer sponsors from October 15, 2018.

### I.1. Scopes of Fast-Track procedure

The FT procedure concerns:

- Clinical trials involving medicinal products (including radiopharmaceuticals)
- All phases in drug clinical trials (phase 0, 1, 2, 3, or 4)
- All therapeutic areas
- **Initial clinical trial authorisation**
- All clinical trial sponsors (academic or private)

The FT procedure does not concern:

- Clinical trials involving medicinal products in the following cases:
  - Having been the subject of a previous submission as part of the VHP (Voluntary Harmonisation Procedure) whether France is the referent NCA or concerned NCA, if and only if France took part in this VHP.
  - Application submitted as part of the PP (pilot phase) procedure, simulating the deadlines of the future European Regulation (EU) no. 536/2014;
  - "Combined" trials aiming to test both the medicinal product and another health product (e.g. Medical device);
- Obligations relating to the conduct and follow-up of clinical trials involving medicinal products including those submitted as part of the Fast-Track procedure (i.e. substantial amendments, reporting of serious adverse events, annual safety reports, new events) and at the end of the trial
- Clinical trials involving innovative medicinal products, i.e.
  - somatic cell therapy medicinal product,
  - gene therapy product

- medicinal product derived from cell or tissue engineering
  - combined innovative medicinal product
  - innovative therapy medicinal products prepared on a non-routine basis
  - medicinal product, all or part of which comprises genetically modified organisms
- Clinical trials involving a health product (other than a medicinal product) especially medical devices, *in vitro* diagnostic medical devices, cosmetics, cell therapy preparations, organs, tissues and labile blood products,
  - Clinical trials not involving health products (especially physiology, physiopathology, behavioural sciences and genetics),
  - Non-interventional trials and research with minor risks or constraints (categories 2 and 3 of the Jardé law).

## I.2. Fast-Track procedure

2 types of Fast-Track are proposed:

|                          | FT 1  | FT2  |
|--------------------------|---|--|
|                          | <b>Access to innovation</b><br>FT1D with additional document of III.2<br>FT1R without additional document of IV | <b>Support for development</b>   |
| Objectives               | Rapid access to advanced therapy products for patients (new substance or new combination) in clinical trials    | Accelerate the implementation of clinical trials for substances or combinations of substances already evaluated by the ANSM            |
| Eligibility criteria     | Early phase trials <sup>[1]</sup><br>Paediatric oncology and paediatric haematology<br>Rare diseases            | Substance or combination of substances already evaluated in France<br>And in the same indication <sup>[2]</sup> as the trial concerned |
| Non-eligibility criteria | Trial on healthy volunteers<br>Complex trial design <sup>[3]</sup><br>ATMP = Advanced therapy medicinal product | 1 <sup>st</sup> trial in France<br>Complex trial design <sup>[3]</sup><br>ATMP = Advanced therapy medicinal product                    |

[1] All early trials: this covers trials managed by the "early phase clinical trials" unit and also the phase 2 trials

[2] or same disease, target population, treatment (symptomatic, curative, preventive, diagnostic); Furthermore pharmaceutical and non clinical data must have already been assessed (no new data submitted in this CT application)

[3] Complex trial design are adaptive CT composed by a "master protocol": initial protocol that defines the frame of the research project (one or more pathologies, more or less homogeneous population, treatments not precisely defined) and in which depending on the availability of new biomarkers or treatments, it could be improve as part of substantial modifications made during the trial to modify the population, indication or add treatments to the study.

## II. METHODS

This procedure is optional, based on a voluntary approach for sponsors (academic or private) and applies to the sponsors' application on a trial by trial basis.

The decisions taken by the ANSM during this procedure will be legally valid.

### III. PROCEDURE FOR IMPLEMENTING A DRUG TRIAL AS PART OF THE FAST TRACK PROCEDURE PROPOSED BY ANSM

#### III.1. Methods for dispatching dossiers

Within the scope of this procedure:

- D0 = date on which the full dossier is received

The CTA must be submitted to ANSM at the following address: [aec-essaiscliniques@ansm.sante.fr](mailto:aec-essaiscliniques@ansm.sante.fr)

#### **Eudralink messaging system (for exchanging with the ANSM)**

The Eudralink secure messaging system proposed by the European Medicines Agency (EMA) should be used (strong recommendation).

To access Eudralink, the user must first make a request to open an Eudralink account (nominative request) with the relevant EMA department by sending an e-mail to the [eudralink@ema.europa.eu](mailto:eudralink@ema.europa.eu), an application form available through the link

[https://eudract.ema.europa.eu/docs/forms/Eudralink\\_Request.doc](https://eudract.ema.europa.eu/docs/forms/Eudralink_Request.doc).

If you use the Eudralink secure method for sending e-mails, it is advisable to:

- set a message expiry date of 90 days and not to select password-protected dispatch
- attach dossier documents in a zipped format (zip or 7z file) without a password.

In order to enable submission to the relevant procedure, "FT1 or FT2" must be stated **in addition** to the other information defined in annex 3 of the "Notice to sponsors of clinical trials on medicinal products, including clinical trials on advanced therapies" on the ANSM's website at the following address: <http://ansm.sante.fr> (Clinical trials section).

|                                      | E-mail subject   |
|--------------------------------------|--|
| First evaluation request             | <b>MED CTA FT1D<sup>(a)</sup> / Phase<sup>(b)</sup> / EudraCT no.<sup>(c)</sup> / Therapeutic area / Concerned EC<sup>(d)</sup></b><br>E.g.: MED CTA FT1D / EudraCT no. 2014-001450-56 / neurology / Est I |
| Answers to validation <sup>(e)</sup> | <b>AR answers / Ref of the application allocated by the ANSM<sup>(f)</sup> / EudraCT no.<sup>(c)</sup></b><br>E.g.: AR answers / MEDAECFT1D-2018-10-00002 / EudraCT no. 2014-001450-56                     |
| Answers to questions <sup>(e)</sup>  | <b>CI answers / Ref of the application allocated by the ANSM<sup>(f)</sup> / EudraCT no.<sup>(c)</sup></b><br>E.g.: CI answers / MEDAECFT1D-2018-10-00002 / EudraCT no. 2014-001450-56                     |

- (a) FT1D if "Access to innovation" Fast-Track with additional document  
FT1R if "Access to innovation" after the "pre-filing" meeting cf § IV  
FT2 if "Support for development" Fast-Track with additional document
- (b) Specify the trial phase
- (c) Specify the trial EudraCT number
- (d) Specify the reference allocated by the ANSM for the application
- (e) Possibly formulated by the ANSM following an assessment of the validation / an assessment of the initial application (question)

The following address should also be used for general questions relating to the Fast-Track procedure : [questions.clinicaltrials@ansm.sante.fr](mailto:questions.clinicaltrials@ansm.sante.fr) completing the "subject" field as follows : **Fast-Track question**

The mail received in the [aec-essaiscliniques@ansm.sante.fr](mailto:aec-essaiscliniques@ansm.sante.fr) mailbox will be sent to the relevant Division according to the scope of competency (see § IV of this document).

## III.2. Dossier content / format

### **III.2.1. Content of the authorisation application dossier submitted to ANSM during the Fast Track procedure**

The application includes:

- An additional document specific to the procedure and completed by the sponsor (according to the Fast-Track procedure: FT1 or FT2)
- A CTA including the documents required according to current regulations transposing European Directive 2001/20/EC. For further information, the sponsor should see the “*Notice to sponsors of clinical trials on medicinal products, including clinical trials on advanced therapies*” on the ANSM’s website at the following address: <http://ansm.sante.fr> (Clinical trials section).

Related to the results relatives to the pharmaceutical quality, chemistry and biology of the medicinal product in which concern to the active substance and the final product:

According to “*Notice to sponsors of clinical trials on medicinal products, including clinical trials on advanced therapies*”, cf p 34/112:

**In the particular case in which the medicinal product’s manufacturer refuse to transmit to the sponsor of the clinical trial the results relatives to the quality of the medicinal product on account of industrial secrets:**

In this case, the sponsor of the clinical trial specifies during the request of CTA submission:

-the results will be transmit directly to the ANSM by the manufacturer. During the transmission of this results to the ANSM, the manufacturer will refer to the requested CTA submission by giving the name of the sponsor of the clinical trial and the EudraCT number. Thus, the manufacturer will fill up the quality section and transmit the FT1D additional document. **The admissibility will take into account the date of reception of this results.**

-the contact point for sending the possible questions from the ANSM related to the quality files. In the absence of indication, they will be sent to the applicant of the clinical trial.

### **III.2.2. Format: Presentation of documents / Language**

It is essential that the sponsor respect the parts naming as described in **annex 3** of the “*Notice to sponsors of clinical trials on medicinal products, including clinical trials on advanced therapies*” on the ANSM’s website at the following address: <http://ansm.sante.fr> (Clinical trials section).

It is imperative that each of the items in the dossier appears in separate files and subfiles.

The documents must be identified by the sponsor and harmonised.

| Identification documents  | Identification  |            |
|---|-----------------|------------|
| <b>Additional document FT1D (or FT2)</b>                          | <b>DOC FT1D</b> |            |
| Cover letter  | LETTER          |            |
| Application form (xml and pdf)                                    | CTAF            |            |
| Trial protocol  | PROTOCOL        |            |
| Protocol summary  | SUMMARY         | Version EN |
| Independent data monitoring committee charter                     | DSMB            |            |
| Investigator brochure<br>Or<br>Summary of product characteristics | IB<br>SPC       |            |
| Documents relating to GMP for the investigational                 | GMP             |            |

|   |             |            |
|---|-------------|------------|
| medicinal product   |             |            |
| Investigational medicinal product dossier                   | IMPD        |            |
| Non-investigational medicinal product dossier               | NIMPD       |            |
| Scientific opinion  | OPINION     |            |
| Paediatric Investigation Plan                               | PIP         |            |
| Contents of the investigational medicinal product labelling | LABELLING   | Version EN |
| Investigational medicinal product importation certificate   | IMPORTATION | Version EN |

### III.3. Evaluation deadlines

It should be noted that the milestones are counted in calendar days.

As part of this procedure:

If a milestone falls on a weekend or bank holiday, the ANSM is expected to respond to the sponsor the last working day before the theoretical milestone date. This also applies to sponsors and to sending responses to the questions raised by the ANSM.

#### III.3.1. Fast-Track 1 “Access to innovation”

The objective is to assess validation within 5 days at most, followed by a 1<sup>st</sup> assessment on D21 at the latest (questions sent to the sponsor) in order to request a response from the sponsor in the event further information is required on D29 at the latest, and in this case to formulate the final response from the ANSM on D40.

It is agreed that the sponsor’s deadline for response is **8 days (at least or at most)**.

| Step  | Milestone dates proposed as part of the FT 1 procedure |
|---|--|
| Validation  | on D5  |
| Assessment with requests for substantiated objections by ANSM | on D21   |
| Sponsor’s response  | + 8D = on D29  |
| Evaluation of the responses by the ANSM and Notification      | +11D = on D40  |

#### III.3.1. Fast-Track 2 “Support for development”

The objective is to assess validation within 5 days at most, followed by a 1<sup>st</sup> assessment on D14 at the latest (questions sent to the sponsor) in order to request a response from the sponsor in the event further information is required on D22 at the latest, and in this case to formulate the final response from the ANSM on D25.

It is agreed that the sponsor’s deadline for response is **8 days (at least or at most)**.

| Step  | Milestone dates proposed as part of the FT 2 procedure |
|---|--|
| Validation  | On D5  |
| Assessment with requests for substantiated objections by ANSM | On D14   |
| Sponsor’s response  | + 8D = on D22  |
| Evaluation of the responses by the ANSM and Notification      | +3D = on D25   |

As part of this procedure:

The milestone dates have been set in relation to the CSIS objectives (Strategic Council of Health Industrie ) **intentionally** for the FT procedure.

Sponsors are to use the procedure on a **voluntary** basis, and the milestone dates stated cannot be legally challenged.

However, all stakeholders shall strive to keep closely to the milestone dates (any deviation from the theoretical milestones shall be followed-up).

### III.4. Validation of the application / acknowledgement of receipt

#### **Purpose of the assessment of the validation of the application**

The validation of the application will focus on the completeness of the dossier (administrative validation, i.e. checking the list of components to be submitted in support of the application, appropriate electronic version, documents drafted in the appropriate language).

The validation of an application is examined by ANSM within 5 days of receipt of the application by mail.

A letter will be sent to the sponsor. If the application is admissible, the admissibility letter shall come with a document specifying the schedule of the theoretical milestone dates specific to the processing of the application in question.

The letter shall be sent by e-mail, by the relevant Division:

- to the sponsor
- with a copy to the relevant EC (if applicable)

### III.5. Dossier assessment

#### **Assessment scope by the ANSM**

The assessment will be carried out to check the safety of persons taking part in the trial, paying particular attention to the safety and quality of the products used in the trial, in accordance with current standards, conditions regarding their use and the safety of subjects in view of the procedures implemented and the methods used as well as subject follow-up.

### III.6. Correspondence from ANSM in the event of questions

#### **In the case of questions from the ANSM**

The letter shall be sent by e-mail, by the relevant Division:

- to the sponsor
- with a copy to the relevant EC (if applicable)

As in the current conventional procedure, the sponsor shall be asked to acknowledge receipt of the letter containing the questions sent to them by e-mail to the relevant Division.

### III.7. Sponsor's responses to questions that may be asked by the ANSM

#### **Presentation of documents**

The documents should be gathered according to the subject's matter and questions raised:

- pharmaceutical data;
- non-clinical data;
- clinical data, etc.

### **Response sent to the ANSM**

The sponsor's response to the ANSM's requests must be sent to the ANSM within the set deadline. Responses sent by e-mail should be sent to: [aec-essaiscliniques@ansm.sante.fr](mailto:aec-essaiscliniques@ansm.sante.fr). It is very important to properly fill in the e-mail "subject" header using the wording in section III.1. of this document in order to facilitate administrative management of the letter.

In the event that the sponsor is not able to provide the answers to ANSM's questions within the maximum 8-day period, as provided by the procedure, the sponsor will be informed that the application will not be managed according to the timetable of the Fast-Track procedure but will be instructed within the regulatory deadlines (60 days maximum).

### **III.8. Final notification**

The letter shall be sent by e-mail, by the relevant Division:

- to the sponsor
- with a copy to the relevant EC (if applicable)

#### IV. ALTERNATIVE PRE-FILING MEETING FOR FT1 ONLY

As part of this Fast-Track procedure, an alternative procedure is offered to sponsors for **trials eligible for the FT 1 procedure (access to innovation) only.**

Therefore, the applicant/sponsor has the possibility to come and present his research project before submitting the application (and in this case, the FT1 additional document does not have to be used).

To do this, the applicant must proceed as follows

1. he must send an e-mail to the address [questions.clinicaltrials@ansm.sante.fr](mailto:questions.clinicaltrials@ansm.sante.fr) while:
  - 1.1. completing the "subject" field as follows : **Request for FT 1 pre-filing meeting**
  - 1.2. Enclosing a copy of the completed CTA letter (according the format recommended by ANSM)
  - 1.3 Mentioning in the e-mail body:
    - a) the scheduled date of submission of the CTA (NB: this date must be 2 to 6 weeks after the sending of this e-mail)
    - b) if the research project was conducted by institutional support to innovation; which means through institutional research programs including:
      - PRT-H: Translational research program in health*
      - PRT-K: Translational research program in cancer*
      - PHRC-N: National clinical research program*
      - PHRC-K: National clinical research program in cancer*
      - PHRC-I: Inter-regional clinical research program*
      - PRME: Medico-economic research program*
      - PREPS: Research program on the performance of the care system*
      - PHRIP: Nurse and paramedical research programs*

This criteria could be taken into account in the priority assignment in the schedule of pre-filing meeting.

2. within 48h, the applicant will receive the "pre-filing" meeting date based on the time slots proposed by the ANSM (a 1-hour slot is offered for 30 min presentation and around 15 min of exchanges).

At this stage, it will also be possible to identify some points of the project that will be specified by the sponsor during the "pre-filing" meeting (in order to provide a framework for the presentation that will be made).

Based upon the files and according to the request of the sponsor, a conference call could be proposed instead of the meeting of "pre- filing " (slot of 1 hour). In this case, the presentation of the project will be transmit by e-mail at the address [questions.clinicaltrials@ansm.sante.fr](mailto:questions.clinicaltrials@ansm.sante.fr) 24 hours before the date of the conference call.

3. on the day of the "pre- filing" meeting, the applicant shall present their project (especially trial indication, target population, primary objective, trial design, monitoring and follow-up expected for the target population). (electronic version as power point preferentially).

Exchanges may be done in French or English.

The number of people expected in face-to-face meeting should not exceed 3-4 people.

It should be noted that during these meeting, the ANSM shall not take a stance as to the outcome of the evaluation during the session: the ANSM offers to discuss especially the eligibility of the application in the Fast-Track procedure, to recall the main safety and quality requirements to be met by the sponsor in their research project, and to confirm the organisational methods for the management of the trial.

The electronic presentation of the project must be sent to the ANSM at the end of the "pre-filing" meeting

4. On the agreed date, the applicant sends the CTA to the e-mail address [aec-essaiscliniques@ansm.sante.fr](mailto:aec-essaiscliniques@ansm.sante.fr)
- a) including the following wording in the e-mail "subject": **AEC MED FT1R / Phase / EudraCT n° / Therapeutic area / Concerned EC / relevant Division** (as approved in the meeting)
  - b) mentioning in the body of the email the pre-filing date where the file was presented

## V. SUMMARY TABLE OF DIALOGUE BETWEEN THE SPONSORS AND THE ANSM

| Steps                                 | Direct submission with additional document for FT1D and FT2  | Pre-filing before the submission Without additional document for FT1R only  |
|---------------------------------------|--|---|
| <b>Pre-submission meeting request</b> | Not applicable   | <p><b>E-mail</b> <a href="mailto:questions.clinicaltrials@ansm.sante.fr">questions.clinicaltrials@ansm.sante.fr</a></p> <p><b>E-mail subject</b><br/>Request for Fast-Track 1 pre-filing meeting</p> <ul style="list-style-type: none"> <li>- CTA letter</li> <li>- provisional date of submission</li> <li>- with mention of institutional support for innovation where appropriate</li> </ul> |
| <b>Pre-submission</b>                 | Not applicable   | <p><b>Meeting</b> (30 min presentation)<br/>no positioning as to the outcome of the evaluation</p> <ul style="list-style-type: none"> <li>- eligibility of the application for FT</li> <li>- main project safety / quality requirements</li> <li>- organisational management methods</li> </ul> <p>(Division concerned + date of CTA submission)</p>  |
| <b>Submission</b>                     | <p><b>E-mail</b> <a href="mailto:aec-essaiscliniques@ansm.sante.fr">aec-essaiscliniques@ansm.sante.fr</a></p> <p><b>E-mail subject</b><br/>MED AEC <b>FT1D or FT2</b> / EudraCT no. / Therapeutic area / Relevant EC</p> <p><b>Application</b><br/>CTA<br/>+ Additional document (FT1 or FT2)</p> <p><b>Date of Submission:</b> free</p> | <p><b>E-mail</b> <a href="mailto:aec-essaiscliniques@ansm.sante.fr">aec-essaiscliniques@ansm.sante.fr</a></p> <p><b>E-mail subject</b><br/>AEC MED <b>FT1R</b> / EudraCT no. / Therapeutic area / Relevant EC</p> <p><b>Application</b><br/>CTA</p> <p><b>Date of submission:</b> as agreed in meeting</p>  |

## VI.GLOSSARY

|                |   |
|----------------|---|
| CTA            | Clinical Trial Authorisation  |
| ANSM           | Agence nationale de sécurité du médicament et des produits de santé-National Agency for the Safety of Medicines and Health Products   |
| AR             | Acknowledgement of Receipt  |
| IB             | Investigator Brochure   |
| IC             | Intermediate letter (questions letter)  |
| EC             | Ethics Committee  |
| NIMPD          | Non-investigational medicinal product dossier   |
| IMPD           | Investigational medicinal product dossier   |
| EudraCT        | European clinical trials database   |
| CTAF           | Clinical trial authorisation application form   |
| EudraCT number | European unique identifier from the European clinical trials database   |
| PIP            | Paediatric Investigation Plan   |
| SPC            | Summary of product characteristics  |
| VHP            | Voluntary Harmonisation Procedure (Coordinated evaluation of multinational medicinal product clinical trials in Europe) <a href="http://ansm.sante.fr/Activites/Essais-cliniques/CTFG-et-Evaluation-coordonnee-des-essais-cliniques-multinationaux-de-medicaments-au-niveau-europeen-VHP">http://ansm.sante.fr/Activites/Essais-cliniques/CTFG-et-Evaluation-coordonnee-des-essais-cliniques-multinationaux-de-medicaments-au-niveau-europeen-VHP</a> |

### ANSM Divisions involved

|  |   |
|--|---|
| <b>ONCOH Product Division</b>                                | Team in charge of haematology, immuno-transplantation, nephrology medicinal products  |
|  | Team in charge of oncology medicinal products   |
|  | Team in charge of haemovigilance, labile blood products, cell therapy and radiopharmaceutical products                        |
| <b>CARDIO Product Division</b>                               | Team in charge of cardiovascular, thrombosis, metabolism, rheumatology and stomatology medicinal products                     |
|  | Team in charge of endocrinology, gynaecology, urology, chest medicine, ENT, allergology medicinal products                    |
| <b>NEURHO Product Division</b>                               | Team in charge of neurology, psychiatry, anaesthesia and alcohol addiction medicinal products                                 |
|  | Team in charge of pain control, nonsteroidal anti-Inflammatory agents, ophthalmology and smoking addiction medicinal products |
|  | Team in charge of narcotics, psychotropic and drug addiction medicinal products   |
| <b>INFHEP Product Division</b>                               | Team in charge of virology and gene therapy medicinal products  |
|  | Team in charge of vaccines and antibiotic, antifungal and antiparasitic medicinal products                                    |
|  | Team in charge of dermatology, hepatogastroenterology and rare metabolic diseases medicinal products                          |
| <b>Authorisation and Innovation Policies Division (DPAI)</b> | Public policies and innovation processes unit<br>(Team in charge of processing early phase clinical trials)                   |

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