

Division on Evaluation of Special Status Medicinal Products and Clinical trials
Clinical trial unit on medicinal products and non health products

**Adjustment of the clinical trial authorisation process regarding clinical trials on
medicinal products by Afssaps**

“Multiple Intermediary Letters (MIL) Procedure”

Version n°1

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Purpose of the MIL procedure

The purpose of this MIL procedure is to reduce, in a significant manner, the time to approval of clinical trials applications (CTA) on medicinal products (in this respect, it is reminded that the CTA's admissibility review period is included in the assessment period allotted to Afssaps).

For this purpose, it is proposed to sponsors, who would demand this procedure to be applied to their trials, that the requests / questions raised by Afssaps during the CTA assessment will be sent to them gradually, as the assessment proceeds, rather than a unique global list of questions sent at the end of the total review of the CTA.

Indeed, at Afssaps different assessors, competent in various fields covering pharmaceutical quality, viral safety, non-clinical and clinical aspects, are in charge of a CTA assessment.

The assessment conclusions of each of the different assessors, either favourable or requesting further information or modifications, are established at different time points. According to the regulation (articles L. 1123-8 and R. 1123-32 of the French public health code), these conclusions are addressed to the sponsor by one unique Intermediary Letter (called IL) when all conclusions of each fields are available.

Besides time to approval reduction, this MIL procedure aims also for:

- addressing earlier to sponsors the questions field by field (pharmaceutical quality, viral safety if applicable, non-clinical, clinical issues), gradually raised by respective assessors ;
- allowing sponsor, in general way, having more time to answer the questions as compare to non-MIL procedure.

Afssaps will proceed to regular reports of this procedure, particularly in order to assess its impact on the CTA time to approval.

Scope

This procedure is optional and applies only:

- upon sponsors' request;
- to CTA applications on medicinal products, excluding gene and cell therapies, whatever the development phase of those trials (from phase I to phase IV included);

Coming into force of the MIL procedure / Diffusion

The MIL procedure will come into force from September 1st, 2010.

This procedure is published on the Afssaps website.

This procedure will be integrated lately in the Afssaps notice to sponsors for clinical trials on medicinal products.

Request for the MIL procedure by sponsors

This procedure is only applied to trials for which the sponsors have made the request, trial by trial.

This request is to be made, for a given trial, during the CTA submission, in the covering letter (in the free text section).

NB: when sponsors have not requested the MIL procedure to be applied, any questions or requests for changes will be addressed to them at once, in accordance with the current regulation.

Description of the procedure

Once the conclusions of the assessment of one of the fields are available, these conclusions are sent by fax to the sponsor in the first Intermediary Letter and a timetable for the response is set.

In the first Intermediary Letter, the progress of the assessment of other fields is indicated ("assessment in progress" or "no question").

Questions regarding other fields are sent to the sponsor by fax in a second Intermediary Letter, or in a third Intermediary Letter. The last set of questions is in principle sent around Day 30.

It is the responsibility of sponsors to answer these questions, Intermediary Letter by Intermediary Letter, within the timetables fixed on each of the Intermediary Letters and not as a single package once all Intermediary Letters have been sent.

The timetables allocated to sponsors are similar to the ones applied outside the MIL procedure. However, for questions requested very early, Afssaps may allocate a longer timetable.

When Afssaps sends a second or third Intermediary Letter, the questions previously raised are not noted again, but the mention "previously asked questions" will be included.

NB: only one set of questions will be sent to the sponsor for one field of assessment.

The conclusions of Afssaps, following the assessment of sponsor's answers to questions, are sent to the sponsor at once, at the end of the process, by sending an authorization for the clinical trial if these answers are considered acceptable.

Particular case

The objective of MIL procedure is to allow the transmission of the conclusions of Afssaps' assessment of each fields once they are available. Each one of the concerned fields (i.e. pharmaceutical quality, viral safety, non-clinical, and clinical) are distinct.

However, in certain rare situations, the conclusions of the assessment of a given field can have consequences in another field. In these particular cases, the questions will be formulated in the section of the Intermediary Letter corresponding to the field of these original questions.

Thus, for example, the conclusions on the assessment of the data related to pharmaceutical quality of the medicine can unveil impurities likely to be genotoxic, not described in the non-clinical part of the CTA dossier, and for which non-clinical complementary requests can be formulated by Afssaps (eg : request for genotoxicity tests). In this case, if non-clinical questions were already formulated at the time of the preceding Intermediary Letter, the complementary requests raised during the assessment of pharmaceutical quality data, although having a non-clinical range, will be formulated in the section relating to the “pharmaceutical quality” field and not in the section relating to the “non-clinical” field.

In the same way, the conclusions of the assessment of the non-clinical data can, in rare situations, lead to a request for modification of the protocol. These requests will then be formulated in the “non-clinical” section of the Intermediary Letter, and not in the “clinical” section, although modifications of the protocol were formulated.

Adjustments in the way to provide answers and in the answers’ calendar can be required by sponsors in these rare instances. The sponsors will then be invited to communicate to Afssaps their difficulties/requests by email to: contact-essaiscliniques@afssaps.sante.fr .

Questions regarding the MIL procedure

- General interest questions relative to the application modalities of MIL procedure are to be addressed to: essaiscliniques@afssaps.sante.fr specifying in object of the email “procedure MIL questions”.
- The questions relative to follow-up of files presented within the framework of MIL procedure (i.e. answering modalities, need to contact Afssaps in order to clarify the put questions, difficulties coping with reply deadline) are to be addressed to: contact-essaiscliniques@afssaps.sante.fr . Regarding these questions, answers will be brought about by Afssaps in 24/48 hours.

Example of application of the MIL procedure

The example presented here is that of a medicine clinical trial for which the assessment procedure of the CTA application by Afssaps is the following :

- conclusions on the assessment of the pharmaceutical quality data available on D10: questions;
- conclusions on the assessment of non-clinical and clinical data favourable on D35, straightaway (without any requests or questions).

In this example, if the MIL procedure is not applied, the Intermediary Letter listing the questions raised by the assessment of pharmaceutical quality data will be transmitted to the sponsor only at D35, once all conclusions of the various assessments are available. The sponsor’s answers will be required at D45. If the provided answers are satisfactory, an authorization can be delivered around D50/J55.

If the MIL procedure is applied to this dossier:

- an Intermediary Letter detailing questions on pharmaceutical quality will be transmitted to the sponsor at D10. For this Intermediary Letter the answers will be expected not later than D25.
- if the answers brought to this Intermediary Letter are acceptable, an authorization can be delivered around D35.

In this example, the application of the MIL procedure would have saved 15 days.