

Detailed guidance for National Scientific-Technical Advice (STA) requests:

(Version 1.1)

1. Introduction:

The DG PRE-Authorisation of the Federal Agency for Medicines and Healthcare Products (FAMHP) in Belgium offers applicants the possibility to request national scientific and/or technical (eg. regulatory) advice (STA) related to the research and development of human or veterinary drug products in view of potential clinical trial applications (CTA's), marketing authorization applications (MAA's) or introduction of variations to marketed drug products. The FAMHP's main objective in providing STA to applicants at a national level is to promote and facilitate as much as possible the development of new drug products from a regulatory perspective in order to enhance the availability of innovative drug products to patients.

For this purpose the FAMHP has implemented a new, centralized and transparent service within the agency which should ensure the processing of national STA requests in a timely fashion while assuring full confidentiality and potential conflict of interest of the involved experts. The FAMHP also aims to provide a consistent follow-up of previous national and European advices (eg. through its interface with the SAWP and SAWP-V at the EMA) in order to assure the quality and consistency of the national



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STA's issued by the FAMHP.

The national STA may be provided to sponsors of clinical trials, pharmaceutical/biotech companies (eg. small biotech spin offs, global companies), research centres, etc.

As the progress in science and subsequently the scientific/regulatory guidelines are constantly evolving over time, the national STA issued by the FAMHP is to be considered as NOT legally binding with regard to any future, related application (eg. CTA's), neither towards the FAMHP, nor to the applicant. The advice given by the FAMHP is based on the questions and information submitted by the applicant at the time of the STA request and can not account for any future changes in science and the scientific / regulatory guidelines. After an initial STA request has been addressed by the FAMHP, applicants are free to submit at any time a follow-up STA request (eg. whenever they feel the need to seek advice on new development data that have been obtained, changes in scientific / regulatory guidelines have taken place, etc).

National STA requests may be submitted to the FAMHP at any time, independently from other ongoing or planned applications (eg. CTA's, MAA's, SAWP advices, PIP's). Nevertheless, applicants are strongly being recommended to seek the FAMHP's advice well in advance of a forthcoming application.

The FAMHP also wishes to point out that a national STA related to a forthcoming application (eg. CTA, MAA, ...) that the applicant plans to submit in the near future is NOT to be considered as a preliminary assessment or approval of the planned application.

The objective of this Guidance is to provide applicants with information regarding the planning and submission of national STA requests in order to ensure an effective and efficient handling of the advice requests throughout the procedure. In particular, guidance is given regarding the conditions, timelines and rules of procedure as well as the scope for requesting national scientific-technical advice to the FAMHP.



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2. Legal basis:

Article 6sexies of the Belgian Medicines law of March 25th 1964 forms the legal basis of the conditions and rules under which the FAMHP can provide scientific or technical advice regarding the research and development of medicines in view of future CTA's, MAA's or introduction of variations to marketed drug products. In addition, Article 4 of the Law of July 20th 2006 regarding the instauration and functioning of the FAMHP clearly states that scientific advice to applicants falls within the competence of the agency.

Moreover, Article 13bis of the Belgian Medicines law of March 25th 1964 together with the Royal Decree of March 31th 2009 forms the legal basis for the fees charged by the FAMHP to applicants submitting a request for national STA.

3. Definitions - Scope:

As defined in the Royal Decree of March 31th 2009 the following types of advice fall within the legal scope of a national STA submitted to the FAMHP:

3.1. FULL STA advice:

A FULL STA advice request is defined as: Advice requests representing a set of multiple, specific questions regarding:

- (1) scientific issues related to research and development
- (2) technical-regulatory issues for which no (national or European) legislation, guidelines exists or the current legislation, guidelines are insufficient.

and for which multidisciplinary expertise is normally required to address the raised question(s).

In general, FULL STA requests would typically cover multiple type of questions (eg. related to quality, preclinical, clinical issues, regulatory, ...) for which multidisciplinary expertise is required. Alternatively, an individual, unidisciplinary question may also represent a complex matter that would require in depth expertise. In such case the advice request can also be

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considered as a **FULL advice request** since it represents a heavy workload.

3.2. AD HOC STA advice:

An AD HOC STA advice request is defined as: Advice requests representing **one specific question** regarding:

- (1) scientific issues related to research and development
- (2) technical-regulatory issues for which no (national or European) legislation, guidelines exist or the current legislation, guidelines are insufficient.

and for which **no multidisciplinary expertise** would normally be required to address the raised question.

Due to its general simple nature, this type of advice request would normally require only expertise in one specific field and would therefore be addressed in writing. However, on exceptional basis, a national STA request submitted by the applicant as an AD HOC advice might be considered by the FAMHP as a FULL advice depending on the complexity of the STA request. In such case, the STA request will follow the procedure of a FULL advice (cfr. paragraph 6.3).

Out of scope:

Depending on the nature and purpose, several type of advice requests / questions fall outside the legal scope of the national STA procedure as these advice request/questions are being addressed by the FAMHP in a different way, according to different procedures, timelines, etc... Addressing such advice requests/questions normally falls within the informative tasks of the FAMHP for which no additional fees are being charged.

The following type of advice request/questions are considered **out of scope** (i.e. non-exhaustive list):



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1. Advice requests:

Advice requests representing one or multiple specific questions regarding technical-regulatory topics for which divergences exist in the current legislation.

2. Frequently asked questions (FAQ's):

Frequently asked questions regarding eg. Submission procedures (eg. CTA's, MAA's, MRP's), general dossier requirements, etc., as described in current national and European guidelines, legislation, etc.

3. Dossier-related questions:

Questions from applicants which are sent to the FAMHP in the context of an application submitted in Belgium (eg. a CTA) fall within the procedure for that particular application and are normally addressed by the involved file manager(s). Subsequently, dossier-related questions fall outside the scope of the national STA procedure.

4. Presubmission meeting requests related to exploratory clinical trials (eCTA's):

Presubmission meetings that are requested by applicants in the context of an eCTA submitted in Belgium, normally fall within the eCTA procedure as described in the Belgian guideline on exploratory clinical trials with investigational medicinal products (IMP's). Subsequently, pre-submission meeting requests related to eCTA's fall outside the scope of the national STA procedure.

However, in case that specific questions would arise during a presubmission meeting related to an eCTA that would technically fall within the scope of a national STA, the applicant will be recommended to seek national STA from the FAMHP in time.

5. Presubmission meeting requests related to marketing authorization (MA):

At current, requests for a presubmission meeting related to new MA applications, line-extensions or variations are only being accepted in case Belgium acts as reference member state (RMS) in the MRP/DCP or when



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Belgian acts as rapporteur / co-rapporteur in the centralized procedure (CP). Such meetings fall outside the scope of the national STA procedure as they are being addressed in a separate procedure. However, in case that Belgium acts as concerned member state (CMS) in the MRP/DCP, the FAMHP offers applicants the opportunity to use the national STA procedure to raise scientific-technical (eg. regulatory) questions in preparation of the MRP/DCP (i.e. as long as the questions fall within the legal scope of a national STA request).

6. Portefolio meetings:

Applicants are also allowed to request for a Portefolio Meeting with the agency. This type of advice meeting typically provides the opportunity for pharmaceutical companies to present an overview of one or several development programs, therapeutics areas in which the company is actively involved, different products (or classes thereof) which are in the development pipeline, etc... In addition, the portefolio meetings allow clarifying the agency's interest for a role in a forthcoming European procedure for specific drug products. This information forms an important basis for the long-term recourse planning of the agency. This type of meeting is considered to fall outside the scope of a national STA request and therefore no fee will be charged to the applicant for a portefolio meeting.

However, in case that the applicant would seek advice on specific scientific and/or technical-regulatory aspects (eg. related to an individual development program), such advice is considered to fall within the scope of a national STA request as this would rather be discussed in a specific advice meeting. Thus, the need for a subsequent specific STA meeting may be the result of a Portefolio Meeting; this advice needs to be applied for separately.

4. Areas of advice:

In general, a national STA request submitted to the FAMHP may cover multiple questions related to a broad range of areas in the field of research and development of drug products. A non-exhaustive list of examples is

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given below:

- Quality aspects
- Pre-clinical aspects
- Clinical aspects
- Technical-Regulatory issues
- GMP-related aspects
- Design and conduct of clinical trials
- Pharmacovigilance aspects
- Risk-management aspects
- ...

National STA requests may be (1) related to the research & development of specific drug products (i.e. drug products falling within the legal definition of a medicinal product) or a class of drug products or (2) may cover more general, non-product related aspects (eg. regarding genotoxic impurity testing).

National STA requests which are related to a specific drug product or class of drug products may cover different types of drug products: chemical, radiochemical, bio(techno)logical, GMO's, paediatric medicines, etc.

5. Timing of STA requests - Type of meetings:

5.1 Introduction:

Scientific-technical advice can be requested during any stage of the initial development of the medicinal product (eg. before submission of a CTA, MAA), and also during the pre-submission period for a variation to an existing marketing authorisation. Meetings can also be held with the FAMHP to discuss pharmacovigilance issues, proposals for changes to labelling or package leaflets, etc.

In conclusion, the following type of STA meetings with the FAMHP can be organised throughout the product lifecycle:



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1. Advice meetings:

≤ Phase 1 (FIM, exploratory CTA's)

≤ Phase 2

≤ Phase 3

Phase 4: post marketing autorisation (MA)

2. Presubmission meetings: (pre MA or pre variation)

Evidently, for most of the abovementioned type of meetings, the applicant would need to submit a FULL STA request to the FAMHP (cfr. paragraph 6.3).

5.2 Initial / follow-up STA requests:

As mentioned before, after an initial STA request has been addressed by the FAMHP, applicants are free to submit at any time a follow-up STA request (eg. whenever there would be a need to seek advice on new development data that have been obtained, when changes in scientific / regulatory guidelines have taken place, etc).

Independently, of the (FULL/AD HOC) procedure that was applied during the initial STA request, any follow-up STA request may be treated by the FAMHP either as a FULL or AD HOC advice depending on the scope of the follow-up STA request. Subsequently, the same fees apply for a follow-up STA request as for an initial STA request submitted to the FAMHP.

5.3 Clarification requests:

On some occasions, it is conceivable that the applicant requests for a clarification of the formal advice issued by the FAMHP in the context of an initial or follow-up STA request. In such cases, no additional fee will be



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charged for the clarification given by the FAMHP. The clarification of an advice may be dealt with either in a meeting with the applicant or in writing. However, such clarification is strictly limited to the questions and issues that were addressed during the FULL or AD HOC advice procedure (i.e. either in a face-to-face or teleconference meeting or in writing). New questions that have arisen from the issued FAMHP advice should be dealt with in a follow-up advice request.

6. Procedure and timelines:

6.1 Introduction:

In order to allow the FAMHP to provide a pointed advice within the foreseen time limits, applicants who intend to seek scientific and / or technical (regulatory) advice from the FAMHP, are requested to strictly follow the procedures described below.

- Any official request for national STA falling within the legal scope of a FULL or AD HOC advice as mentioned above should be submitted to the Directorate-General PRE-authorisation of the FAMHP.

These requests should be sent electronically to our central mailbox: sta@fagg-afmps.be. Alternatively, (eg. in case large electronic files above 5 MB would be submitted), electronic STA requests can also be sent on CD-rom or USB key).

In addition, applicants are asked to send at least two hard copies of the national STA request by post to the following address :

Federal Agency for Medicines and Health Products
Directorate-General PRE-authorisation (desk 8D222)

Victor Hortaplein 40/40
B-1060 Brussels
BELGIUM

To the attention of: Ms. Greet Musch

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6.2 Payment information:

- Each submitted STA request must be accompanied by payment of the appropriate fee (cfr. Paragraph 9 below). Each FULL STA request requires payment of € 1976,15 and each AD HOC STA request requires payment of € 197,61 regardless if the request concerns an initial or follow-up STA request. Payment must be made on the following bank account nr. of the FAMHP: 679-0021942-20

Contact details of the bank:

Poste financière

Chaussée d'Anvers 59

B-1100, Bruxelles (Belgium)

IBAN : BE28 6790 0219 4220

BIC : PCHQBEBB

Applicants should clearly mention on the bank statement if the application concerns a "FULL or AD HOC STA request" and if it concerns an initial or follow-up STA request; followed by the name of the applicant.

For payments from abroad the transfer fees should be paid by the payer. Applicants are also requested to include a proof of payment (eg. a bank statement) to the STA request since this is verified during the validation of the STA request.

For each initial or follow-up (FULL/AD HOC) STA request a separate payment should be made.

In case that an inappropriate fee was paid by the applicant which does not correspond to the fees defined in paragraph 9 below (eg. when submitting the STA request under the wrong procedure), the applicant will be contacted in order to make the appropriate payment.

In case the applicant should ask for a withdrawal of his STA request after payment of the fee (as part of the formal submission to the FAMHP), the fee

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will not be refunded by the FAMHP.

When a formally submitted STA request is declared invalid by the FAMHP at the end of the validation phase of the procedure (cfr. Paragraph 6.3 below), the fee will be refunded to the applicant.

6.3 Procedures and timelines:

In general, national STA requests submitted under the FULL or AD HOC advice procedure will follow during the respective procedure the three steps outlined below:

Step 1: Validation phase

During validation of a FULL or AD HOC STA request, the FAMHP will verify if the following criteria are met:

- the submitted STA request falls within the legal scope of a national STA request
- the submitted STA request has been correctly submitted by the applicant under the FULL or AD HOC procedure
- the appropriate fee has been paid
- all supportive documentation is included in the submitted STA request (cfr. Paragraph 7 below)
- a clear and solid motivation for seeking national scientific-technical advice is provided by the applicant

The validation phase only begins when the Directorate-General PRE-authorisation of the FAMHP has received the formal STA request (including all supportive documents) and the proof of payment from the bank.

Based on the received supportive documents and depending on the complexity and nature of the raised questions, the FAMHP will verify if the submitted STA request fulfills the definition of a FULL or AD HOC STA request and subsequently if a meeting at the agency would be necessary (i.e. Full advice) or if a written advice will be given (i.e. Ad Hoc advice). Nevertheless, it is the applicant's responsibility to submit the STA request under the appropriate procedure.

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The applicant will be informed about the validation of the STA request. Any refusal to validate the STA request will be communicated to the applicant as soon as possible. Grounds for refusing validation of the STA request may be: eg. insufficient/missing motivation of the STA request, insufficient/missing supportive documentation, inappropriate payment of the fee, the requested STA may fall outside the legal scope of national STA, etc.

Shortcomings which can not be resolved by the applicant will automatically lead to an INVALID application. In contrast, when all shortcomings can be resolved by the applicant during validation phase, the STA request will be declared VALID (= Day 0). As soon as all validation criteria are being met, the valid STA request will enter the evaluation phase of the FULL or AD HOC STA procedure (cfr. step 2).

Step2 : Evaluation phase

During the evaluation phase of a valid STA request, the appropriate internal and/or external experts of the FAMHP are being selected and designated by the STA coordinator. Subsequently, the content of the STA request is being evaluated by the designated experts in view of addressing the questions raised by the applicant. The questions contained in the STA request will be formally addressed by the FAMHP as follows:

FULL STA requests:

In principle, a valid STA request falling within the definition of an FULL advice will be addressed by the FAMHP in a face-to-face meeting or through a teleconference meeting with the applicant. Depending on the nature and complexity of the FULL STA request, the applicant is free to propose which type of meeting he prefers with the FAMHP. However, the FAMHP generally prefers a face-to-face meeting for discussing FULL STA requests. FULL STA advice requests will be addressed by the FAMHP in a face-to-face meeting or teleconference meeting within 70 days^(*).

As a general rule, the FAMHP foresees 1.5 hours (max. 2 hours) for advice meetings with applicants. If necessary, the applicant is allowed to provide a brief presentation during the meeting with the FAMHP, however this should be limited (eg. 15 min). Such presentation may cover eg. an overview of the



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issues to be discussed, background information on the development of the drug product which is relevant to the meeting, etc.

If the applicant wishes to give a presentation during the meeting, this should be communicated to the FAMHP well in advance (eg. 14 days prior to the meeting) in order to ensure the availability of the required technical equipment in time.

The meetings are chaired by the FAMHP and the discussions are normally being held in English. The applicant is free to bring in experts for attending the meeting as long as this is properly being communicated well in advance (i.e. through the attendants list). Nevertheless, it is the responsibility of the FAMHP to select and designate the internal and/or external experts that will provide the formal advice on behalf of the FAMHP.

Prior to the meeting the applicant will be asked to draft up the meeting minutes (i.e. in English). After the STA meeting has taken place, the applicant should send an electronic copy of the draft meeting minutes to the FAMHP within 14 days following the STA meeting. The meeting minutes will be validated by the involved STA coordinator and experts in order to ensure the consistency and completeness of the minutes in relation to the discussions held during the formal STA meeting. Afterwards, the finalized meeting minutes (including any additional comments and/or corrections from the FAMHP) will be sent back to the applicant within 14 days following receipt of the draft meeting minutes.

AD HOC STA requests:

In principle, a valid STA request falling within the definition of an AD HOC advice will be addressed by the FAMHP in writing, within 30 days^(*).

As mentioned before (cfr. Paragraph 3), this type of advice request will normally be addressed in writing due to its simple nature and the minimal workload associated with such STA request. However, on exceptional basis, a national STA request submitted by the applicant as an AD HOC STA request might represent a very complex question that would require in depth expertise from the FAMHP. Taken into account the complexity and heavy workload associated with such advice request, this dossier would be

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considered by the FAMHP as a FULL STA request rather than an AD HOC STA request. In such particular case, the STA request will follow the procedure of a FULL STA request.

(*) Date counting from the day at which the STA request was formally declared VALID by the FAMHP (= Day 0). These timelines represent the maximum period during which the FAMHP commits itself to provide a pointed advice to the applicant. Evidently, the FAMHP aims to address all advice requests from applicants as fast as possible after validation .

Step 3: Administrative phase

After the validated meeting minutes (i.e. for a FULL STA request) or the written advice (i.e. for an AD HOC STA request) have been sent back to the applicant and no further clarification are requested by the applicant, the procedure is officially being closed.

Along with the validated meeting minutes or the written advice, a qualitative feedback questionnaire will be sent to the applicant (cfr. paragraph 8 below) which can be completed by the applicant on a voluntary basis.

7. Content & format of STA requests:

7.1 introduction:

Detailed information on the content and format of national STA requests submitted to the FAMHP can be found on the website.

7.2 Application form:

As part of the required content of a national STA request, applicants are being requested to download the electronic application form in access format (cfr. annex below) and to include (1) the completed electronic



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document in the STA request that will be submitted electronically and (2) to send a paper copy by post to the FAMHP. (cfr. the electronic application form can be printed out upon completion in access).

The electronic application form is intended to contain all essential information related to the national STA request that would provide the FAMHP with complete and concise data in order to provide a pointed advice.

The use of the electronic application form when submitting a STA request to the FAMHP, is not strictly mandatory. However, in the interest of a fast and efficient processing of the advice requests the applicants are strongly being recommended to use the electronic application form. An electronic copy of the document can be found on the FAMHP website.

8. Feedback questionnaire for applicants

As a federal agency, the FAMHP pays much importance to the quality of the provided national STA's and to the satisfaction of the applicants. In order to improve its national STA service on a continuous basis, applicants are offered the opportunity to fill in a feedback questionnaire after having received the final FULL or AD HOC advice from the FAMHP. The qualitative feedback questionnaire is intended to ask the applicant's opinion on the following three aspects related to the received national STA:

- Quality of the provided national STA
- Quality of the service provided during the STA procedure
- Consistency of the provided national STA with previous advice(s)

Applicants are being asked to complete the feedback questionnaire on a voluntary basis and send it back afterwards to the FAMHP. An electronic copy of the document can be found on the FAMHP website along with the instructions for filling in and sending back the document to the FAMHP.



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9. Fees:

At current, the following fees^(*) apply to requests for national STA submitted to the FAMHP:

FULL STA advice	1976,15 euro
AD HOC STA advice	197,61 euro

The same fees for national STA request will apply independently of the type of applicant by whom the STA request is submitted to the FAMHP: sponsors of clinical trials, pharmaceutical/biotech companies (eg. small biotech spin offs, SME's, global companies), research centres, etc.

The same fees for national STA request will apply regardless of the area of advice (eg. paediatrics, oncology, etc..) or timing of seeking advice at national level (eg. initial versus follow-up advice).

Detailed instructions on the payment of fees for national STA requests can be found in paragraph 6.2 above.

(*) Fees for national STA are subject to indexation on a yearly basis. Indexation of the fees takes place at the beginning of each calendar year.

10. Contact for further information:

Any general or specific questions that applicants may have related to the national scientific and/or technical (regulatory) advice service of the FAMHP can be sent to the following mailbox: sta@fagg-afmps.be

11. Legal texts:

11.1 Laws:

- Medicines law of March 25th 1964:

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- Law of July 20th 2006 regarding the instauration and functioning of the FAMHP:

11.2 Royal Decrees:

- Royal decree of March 31th 2009 in execution of article 6sexies of the Medicines law of March 25th 1964:

12. Frequently asked questions (FAQ's):

Under construction

13. Abbreviations:

CTA	Clinical trial application
MAA	Marketing authorization application
MRP	Mutual recognition procedure
PIP	Paediatric investigation plan
SAWP	Scientific advice working party
SAWP-V	Scientific advice working party-veterinary
EMA	European Medicines Agency
DCP	Decentralized procedure
IMP	Investigational Medicinal product
RMS	Reference member state
CMS	Concerned member state