Agenzia Italiana del Farmaco

AIFA

AIFA Guidance for Companies requesting Scientific Advice

INTRODUCTION

This guideline provides an overview of the procedure to obtain a Scientific Advice (hereafter SA) from AIFA and gives guidance to the applicants in preparing their request. This guidance document also explains the scope and nature of the national Scientific Advice.

The SA has the purpose to provide scientific and methodological support to the applicants for the definition and the development of the appropriate tests and studies, including GMP compliance, necessary to demonstrate quality, safety and efficacy of medicinal products and in relation with the appropriateness of the documentation necessary for the envisaged procedure.

SCOPE

The scientific advice procedure applies to those evaluation activities, related to requests for scientific assistance either during the initial development of a medicinal product before submission of a marketing authorisation application for new medicinal products or later on, during the post-authorisation phase (variation procedures). The SA can be requested independently from the authorisation procedure (national, MR, DC, centralised) which will be undertaken.

The SA procedure applies also to the evaluation activities concerning new manufacturing sites and/or production lines designs, as well as applications for scientific opinions on interpretation and/or application of legislation and/or guidelines concerning the manufacturing of medicinal products to guarantee quality standards (i.e. Good Manufacturing Practice).

A Scientific Advice application can be submitted to AIFA in the following cases:

1. During pharmaceutical, nonclinical and clinical development of a product: the Agency intention is to promote early interaction with Companies. In this perspective, a request

arriving at a very late stage of development, does not fall within the scope of a Scientific Advice and therefore it is generally considered not acceptable.

2. Before the development phase of a project: for specific applications and interpretations of guidelines on warehousing, manufacturing and control of medicinal products (i.e. first authorisations, extensions, remodeling of warehouses, production lines, quality control, art 5. D.Lgs 219/06 application);

3. During the post-authorisation phase: for specific requests relating to any part of the dossier (e.g. new formulation development, changes in manufacturing process, clinical development for extension of therapeutic indications, post-authorisation clinical studies etc...);

4. During the execution phase of a project: for the purpose of a continuous correct application of the guidelines on warehousing, manufacturing and control of medicinal products;

5. Follow-up to previous Scientific Advice (SA): a follow-up to the initial request can typically be requested to reconsider the Scientific Advice already given in the light of new information available to the applicant or in case of changes or amendments to the development programme for which Scientific Advice was given, for instance in cases where problems with adherence to the initial opinion occur.

Scientific Advice is related to technical/scientific issues concerning quality, non-clinical, clinical and technology, and may be requested for all medicinal products for human use, as defined in Directive 2001/83 as amended.

Scientific advice may be related also to Health Technology Assessment (HTA) aspects, for relative efficacy and relative effectiveness evaluation. It is possible to ask for joint SA both on HTA and technical/scientific aspects, as well.

Scientific Advice may be provided also for interpretation and implementation of European technical/scientific guidelines or in case no specific European guidelines are available or when the applicant intends to diverge from the development programme foreseen by the relevant guidelines on the grounds of clearly stated reasons.

Scientific Advice is prospective in nature, so it cannot be applied to the evaluation of the results of pharmaceutical, pre-clinical and clinical studies according to Art. 8, paragraph 3, Arts. 10, 10 b), 10 c) or 11 of Directive 2001/83/EC and of Art. 6 of Regulation (EC) n.

726/2004 as amended. These are part of the marketing authorisation procedure and are disciplined by Parts IV and V of the Italian Legislative Decree 219/06 as amended.
Scientific Advice cannot be requested for the evaluation of the validation results of machinery, technological equipment and systems, and/or validations of manufacturing or cleaning processes. These are part of the procedure for application for a manufacturing authorisation according to the Articles in Part IV of the Italian Legislative Decree 219/06 as amended.

AIFA provides technical-scientific state-of-the art Scientific Advice. AIFA undertakes to recognise methodological and scientific conclusions of a Scientific Advice when this is used for the application for a marketing authorisation. It can therefore be included in the Application Form under point 1.2 of the part concerning 'Requirements for a standardised dossier for a marketing authorisation' in Annex I to the Italian Legislative Decree 219/06 as amended. However, Scientific Advice given is not legally binding with regard to either any future marketing authorisation application of the product concerned, or subsequent evaluations in case of inspection or of subsequent assessment within the follow-up phase.
Moreover, the national SA HTA is not legally binding for the Agency for future applications of pricing and reimbursement definition.

Remuneration foreseen for national Scientific Advice are published at AIFA website **(see Annex 301/01)**

The following procedures are out of the scope of this guideline:

- pre-submission meetings related to procedures for which IT acts as RMS
- EMA / HTA Parallel Scientific Advice

Limitations

SA Applications arriving at a very late stage of development, do not fall within the scope of a Scientific Advice, they are rather considered a pre-assessment of the results already obtained or the request of an opinion on how to submit information in the registration dossier or in the file to support applications of pricing and reimbursement definition.
For centralized procedures, questions about how to submit data fall within the scope of the pre-submission meeting.

In the case of centralised procedures, the SAN may not be required in cases where EMA/CHMP has already appointed Italy as Rapporteur or Co-Rapporteur for the procedure for which the SA is requested and/or when the procedure has already started. In cases where Italy acts as Rapporteur or Co-Rapporteur, SAN for the same medicinal product but for different therapeutic indications cannot be issued in conjunction with an on-going EMA procedure. The possible timing overlap should be kept in due consideration by companies in scheduling requests.

In the case of SAN HTA, the procedure can not overlap or take place immediately near the request for pricing and reimbursement definition. The possible timing overlap should be kept in due consideration by companies in scheduling SAN HTA requests so that they can be accepted.

In the case of centralised registration products, the SA HTA only request may be considered even where EMA/CHMP has already appointed a Rapporteur or Co-Rapporteur for the procedure and/or when it is already on-going. However, applications received at very late stage of clinical development should be adequately justified and, in any case, applicants will have to take into account the above mentioned limitations.

OPERATIONAL STEPS

Applicants wishing to apply for scientific advice contacts the Coordinator of the National Scientific Procedures (SA coordinator), to the following e-mail address: scientificadvice@aifa.gov.it (copy: segr.scientifica.dg@aifa.gov.it)

The applicant encloses to the e-mail the application form **Mod. 301/01** "Request for scientific advice-application form" duly filled-in to make clear the subject of the request.

For SA requests relating to the development phases and projects concerning manufacturing sites, **Mod. 301/02** shall be used.

Within 20 working days after application's receipt, the SA Coordinator provides the applicant by e-mail with a response on whether the request for Scientific Advice is acceptable or not, together with a possible timing to start the procedure.

Within 5 working days after the SA co-ordinator's communication, the Applicant confirms (or not) the intention to start. Following the Applicant's confirmation, the administrative contact point appointed for the specific SA procedure sends to the Applicant, by e-mail, a draft contract and an explanatory letter containing all the information to proceed with the payment e to provide AIFA with the necessary documentation to start the SA procedure.

The administrative contact point, by the explanatory letter, informs the Applicant that, should it accept AIFA's conditions and intend to continue to pursue the SA procedure, it shall:

a. complete the attached draft contract with the information concerning the company applying for the SA and the other specific requests;

b. proceed with the payment of the remuneration indicated in the draft contract, according to the instructions specified in the explanatory letter;

c. deliver the original of the documents set out under points a) and b) to the administrative contact point appointed for the specific SA procedure, responsible for the administrative handling of contract. The contract, duly filled-in, should be provided by the Applicant to AIFA in double original copy. Moreover, in case the company declares to be eligible for 25% reduction of compensations foreseen for small and medium-sized enterprises (SMEs), it should provide the administrative contact point with the adequate documentation as proof of its status of SMEs.

The Applicant, who is unable to return the completed and signed contract and pay the payment within 30 calendar days, should inform the administrative contactor of the timing foreseen to comply with such obligations and/or give notice of any waiver of the procedure. In the absence of receipt of the requested documentation/payment or of a communication regarding the timing within 30 calendar days, the procedure will be considered withdrawn.

At the same time as returning the contract enclosing the proof of payment, the applicant shall send to the scientific administrator (the name and contact details are indicated in the explanatory letter), in electronic format (word) all the documentation deemed necessary for the SA evaluation by the appointed experts (briefing document) prepared according to Mod. 301/03, where applicable.

The validation phase of the procedure is considered completed following the briefing document, properly drafted, receipt, and following receipt of the proper administrative documentation consisting in the double original contract duly filled-in, the proof of payment and, where applicable, the proof of SME status.

The a.m. validation phase, performed in advance of sending the contract to the Director General for the signature, lasts not more than 5 working days starting form the documentation receipt, unless the clock is stopped due to the necessity of supplementary information and/or documentation.

Once the application is validated, the administrative contact point sends the contract to the Director General to be signed.

Start of the procedure

The SA procedure starts effectively from the day when the contract is signed by the Director General (day 0) which sets the subsequent timeline, which foresees that the evaluation necessary for issuing an advice does not exceed 90 days.

The administrative contact point sends the signed contract to the Applicant together with the relevant invoice.

Meeting AIFA/Applicant and Final Report

The scientific administrator organises a meeting with the Applicant, to be held about at day 60 of the procedure. The scope of the meeting is to discuss the "draft answer" document sent to the Applicant 5 calendar days in advance of the meeting.

Within 2 working days before the date of the meeting, the Applicant sends to the scientific administrator the list of documents related to the meeting, in particular:

- the list of participants (max allowed number 10), together with their affiliation and role within the Scientific Advice procedure;
- the slides for the presentation of the product focused on the critical issues and the Applicant's points of view.

The presentation should be on electronic support, otherwise the Applicant will have to provide the same number of hard copies as the number of participants in the meeting.

The discussion may take place by teleconference, if necessary.

At the latest five working days after the meeting (day 65-67), the Applicant should send the draft minutes to the scientific administrator for further verification and approval by the AIFA Evaluation team.

Within the same date the Applicant should send to the scientific administrator the possible supplementary documentation following comments raised, if any, by the AIFA experts during the meeting. This to allow the AIFA Evaluation team to draft and officially approve the final report on the basis of the opinions agreed within the Evaluation team and of the results of the meeting with the Applicant.

It should be noted that any supplementary documentation provided after the meeting should have only the scope to provide some more clarification with respect to what is already presented in the Briefing Document and should not be additional documentation to be evaluated *ex novo*.

The SA final report is a document drawn up as answers to the specific initial questions submitted by the Applicant. It will be sent to the Applicant within day 90 of the procedure, together with a transmission letter signed by the Director General of AIFA.

National SA procedure timing

STEP	TIMING (calendar days)
Start (*day when the contract is signed by the DG)*	**day 0**
Draft answer	**day 55**
Meeting	**day 60**
Draft minutes	**day 65-67**
Adopted minutes	**day 75**
Final report	**day 90**

Roma, 27.11.2017

Il Direttore Generale

(Mario Melazzini)