GUIDELINE FOR CONSULTATION OF THE AIFA BY A NOTIFIED BODY ON AN ANCILLARY MEDICINAL SUBSTANCE TO BE USED IN A CLASS III MEDICAL DEVICE

Agenzia Italiana del Farmaco Via del Tritone, 181 - 00187 Roma (+39) 06.59.78.401 www.aifa.gov.it

INTRODUCTION

This guideline provides an overview of the procedure to obtain a Scientific Opinion on ancillary medicinal substances used in a class III medical device requested to the Italian Medicines Agency (AIFA) by notified bodies, and provides guidance to the Notified Body in preparing their request.

SCOPE

This guideline aims to provide interested parties with appropriate information on the procedural aspects as well as the format and data requirements to facilitate the consultation procedure between AIFA and Notified Bodies regarding medicinal substances within the meaning of Article 1 of Directive 2001/83/EC incorporated, as an integral part, in a medical device and which are liable to act upon the body with an action ancillary to that of the device.

LEGAL BASES

- **Article 1(8) of Regulation (EU) 2017/745 :** *"Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorized in accordance with this Regulation."*
- **Annex I, section 12.1 of Regulation (EU) 2017/745 :** *"In the case of devices referred to in the first subparagraph of Article 1(8), the quality, safety and usefulness of the substance which, if used separately, would be considered to be a medicinal product within the meaning of point (2) of Article 1 of Directive 2001/83/EC, shall be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC, as required by the applicable conformity assessment procedure under this Regulation."*
- **Annex IX, chapter II, section 5.2 of Regulation (EU) 2017/745** *: "(a) Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma and that has an action ancillary to that of the device, the quality, safety, and usefulness of the substance shall be verified, by analogy with the methods specified in Annex I to Directive 2001/83/EC.*

  (b) Before issuing an EU technical documentation assessment certificate, the notified body shall, having verified the usefulness of the substance as part of the device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or from the EMA, either of which to be referred to in this Section as 'the medicinal products authority consulted' depending on which has been consulted under this point, on the quality and safety of the substance including the clinical benefit or risk of the incorporation of the substance into the device. Where the device incorporates a human blood or plasma derivative or a substance that, if used separately, may be considered to be a medicinal product falling exclusively within the scope of the Annex to Regulation (EC) No 726/2004, the notified body shall seek the opinion of the EMA.

  (c) When issuing its opinion, the medicinal products authority consulted shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body."

  (d) The medicinal products authority consulted shall provide its opinion to the notified body within 210 days of receipt of all the necessary documentation.

  (e) The scientific opinion of the medicinal products authority consulted, and any possible update of that opinion shall be included in the documentation of the notified body concerning the device. The notified body, shall give due consideration to the views expressed in the scientific opinion when making its decision. The notified body shall not deliver the certificate if the scientific opinion is unfavourable and shall convey its final decision to the medicinal products authority consulted.

  (f) Before any change is made with respect to an ancillary substance incorporated in a medical device, in particular related to its manufacturing process, the manufacturer shall inform the notified body of the changes. That notified

body shall seek the opinion of the medicinal products authority consulted, in order to confirm that the quality and safety of the ancillary remain unchanged. The medicinal product authority consulted shall take into account the data relating to the to the usefulness of incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the risk or benefit previously established concerning the incorporation of the substance into the device. The medicinal products authority consulted shall provide its opinion within 60 days after receipt of all the necessary documentation regarding the changes. The notified body shall not deliver the supplement to the EU technical documentation assessment certificate if the scientific opinion provided by the medicinal product authority consulted is unfavourable. The notified body shall convey its final decision to the medicinal products authority consulted.

(g) Where the medicinal authority consulted obtains information on the ancillary substance, which could have an impact on the risk or benefit previously established concerning the incorporation of the substance in the device, it shall advise the notified body as to whether this information has an impact on the risk or benefit previously established concerning the incorporation of the substance into the device. The notified body shall take the advice into account in reconsidering its assessment of the conformity assessment procedure.

ACCESS TO INFORMATION SYSTEMS AND FEES

For the purposes of accessing AIFA systems, a "Company Users Administrator" (CUA) shall be appointed.
The appointed person, preferably a staff member of the Notified Body, will have access to all applications for which a specific request has been submitted during registration.
Any Notified Body lacking a SIS Code shall preliminarily request to be assigned one by following the procedure specified at the following link: https://www.aifa.gov.it/accesso-sistemi-informatici-aifa
After obtaining the definitive SIS Code, the CUA can register with the dedicated AIFA front-end system, at the following address: https://www.agenziafarmaco.gov.it/registrazione/
The applicable fee can be consulted on the AIFA website at the following link: https://www.aifa.gov.it/tariffe
Fees for Scientific Opinion are proportional to its complexity, taking into account the following elements: whether the active substance manufacturer has already been evaluated by AIFA; whether the EDQM has already granted a Ph. Eur. certificate of suitability to the active substance manufacturer; whether the request of the Notified Body is related to a variation in respect of a previous assessment (post-consultation phase).

CONSULTATION PROCEDURE

a) Pre-submission activities

Prior to the official submission, the Notified Body will need to provide an "*intention to submit letter*" by contacting AIFA at the following e-mail address: scientificopinion@aifa.gov.it.
The e-mail message should include the date of the proposed submission and a duly filled-in scientific explanation (Form 1 - Briefing Document), clarifying whether the Application relates to a *Consultation Procedure* or to a *Supplementary Phase* (see below). In addition, the email should specify the subject of the request and the fact that the action of the medicinal substance incorporated in the medical device is only ancillary to that of the device. The classifications of the device and the components should be in line with the definitions and examples of MDCG 2022-5 April 2022.
Within 15 working days from the applicant's request, AIFA shall provide an acceptance letter.

b) Data requirements and format of the application dossier

The Notified Body shall submit the proof of payment, the Application Form and its annexed documents (see Form 2 – Application Form for Consultation phase and Form 2a – Application Form for Supplementary phase) via the Common European Submission Portal (CESP). The Notified Body is also required to send an email to the following e-mail address: scientificopinion@aifa.gov.it, including the CESP submission number and date.

Guidance on data requirements and format of the application dossier can be found in Appendix I.
Relevant information on the medical device should be presented in a clearly structured manner, following the CTD format (Volume 2B Notice to Applicants Medicinal Products for Human Use – Presentation and Format of the Dossier).
For medicinal substances with an ancillary action that are incorporated in a medical device, the quality, safety and usefulness will be verified by analogy with the appropriate methods specified in Annex I to Directive 2001/83/EC as amended. The intended purpose of the device will be taken into account.
The Notified Body has to provide a report (Appendix I – Section 1 of the dossier) to AIFA, specifying the usefulness of the ancillary medicinal substance as part of the medical device, taking into account the intended purpose of the device. This would ensure that AIFA can give an opinion on the quality and safety of the substance, including the clinical benefit/risk profile of the incorporation of the substance into the device.
According to MDCG 2022-5, the aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

c.1 Initial consultation procedure

The validation phase usually takes no more than 14 working days, starting from the receipt of the documentation via CESP.
During this phase, the receipt and appropriateness of the administrative documentation will be checked and a reference number will be assigned to the procedure. A clock stop will be triggered in case supplementary information is requested by AIFA.
Once the application has been validated, the Notified Body is informed of day 0 (the start date of the technical assessment) and of the relevant timetable. The teams of experts responsible for assessing the submitted dossier will then be appointed.
AIFA will follow the same assessment timetable as used for a new application according to the National Procedure (cf. EudraLex notice to applicants Volume 2A, Chapter 4), that is a 210-day maximum timetable with the opportunity for clock stops for the applicant to reply to the List of Questions.
AIFA will send the Preliminary Assessment Report, including a List of Questions, within 120 days from the start of the technical assessment.

AIFA will issue its final opinion on the quality and safety of the substance(s), taking into account the manufacturing process and the data related to the usefulness of the incorporation of the ancillary medicinal substance, and including the clinical benefit/risk profile of the incorporation of the substance(s) into the medical device. The final opinion is sent to Notified Body by certified e-mail.
The Notified Body shall take into account the opinion of the Competent Authority and use its judgment to either approve the drug/device combination, after considering all risk/benefit aspects of the intended or expected use of the product, or alternatively reject the product.

c.2 Supplementary consultation procedure

Following the initial consultation, any change in the design or manufacture of the device (in particular related to the source, the manufacturing process, the amount and method of incorporation of the ancillary substance) which could have an effect on the quality, safety or usefulness of the medicinal substance in the device should be evaluated.
The Notified Body shall be informed of the changes and shall consult AIFA in order to confirm that the quality and safety of the ancillary substance is maintained. AIFA will take into account the data related to the usefulness of the incorporation of the substance into the device as determined by the Notified Body, in order to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance to the device.

Major or minor amendments to the documentation on an ancillary medicinal substance incorporated in the medical device provided in the consultation procedure dossier will be classified and evaluated by analogy with the Variations Regulation (Commission Regulation (EC) no. 1234/2008).
Examples of amendments that may require a *Supplementary consultation* include:

- Change of supplier of the ancillary medicinal substance or intermediate processor;
- Change to the formulation or grade of the ancillary medicinal substance or intermediate;
- Significant change to the manufacturing process or change to the specification of the medicinal substance as notified by the substance manufacturer;
- Changes to quality control tests relevant to the active substance during manufacture;
- Change of manufacturing process for the incorporation of the medicinal substance into the device;
- Change of packaging;
- Change in the method of sterilization;
- Extension of shelf life (unless stated in the initial dossier that an extension to shelf-life is planned and in the AIFA assessment report that the planned extension of the shelf life would not require a supplementary consultation providing all data are within specification);
- Changes to the intended use of the device;
- Some changes in the design of the device which may impact on the availability or release of the medicinal substance (e.g. device size increase if the quantity of the medicinal substance per device is increased, change in device surface area).

This list is intended for guidance and is not prescriptive or exhaustive. It is the responsibility of the Notified Body to decide if a Supplementary consultation is required, based on the information provided by the manufacturer.

The reference number of the original consultation should be quoted in the new Supplementary consultation request. The target time for the assessment of these applications is 60 days from receipt, but may vary depending on the complexity of the consultation.

The validation phase usually takes no more than 14 working days, starting from the receipt of the documentation via CESP.
During this phase, the receipt and appropriateness of the administrative documentation will be checked and a reference number will be assigned to the procedure. A clock stop will be triggered in case supplementary information is requested by AIFA.
Once the application has been validated, the Notified Body is informed of day 0 (the start date of the technical assessment) and of the relevant timetable. The teams of experts responsible for assessing the submitted dossier will then be appointed.

In general, the timetable is the following:

- 60 days for consultation on a major amendment to the documentation on an ancillary medicinal substance (included the extension of the use of the medical device). AIFA shall send the Preliminary Assessment Report, including a List of Question, within 45 days and shall issue its final opinion within 15 days from the receipt of the requested document, piece of information or clarification.
- 30 days for consultation on a minor amendment to the documentation on an ancillary medicinal substance. AIFA shall send the Preliminary Assessment Report, including a List of Question, within 15 days and shall issue its final opinion within 15 days from the receipt of the requested document, piece of information or clarification.

Changes to the qualitative or quantitative composition relating to the active substance(s), or indications for use etc. would normally be subject to a new, full consultation. Examples include:

a. quantitative change to, addition or deletion of one or more active substances

- replacement of the active substance by another salt/ester complex/derivative;
- incorporation of an additional medicinal substance

b. variations relating to the use of the medical device

- addition of an indication in another therapeutic area;
- addition of or change in the route of administration.

REFERENCES

- Directive 2001/83/EC as amended of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
- EudraLex, Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD).
- Commission Regulation (EC) 1234/2008 of 24 November 2008 as amended by Commission Regulation (EU) 712/2012 of 3 August 2012) concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.
- Regulation (EU) 2017/745 of the European Parliament and of the council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

Rome, 18/03/2024