Agence nationale de sécurité du médicament et des produits de santé

Consultation for a medical device incorporating an ancillary medicinal substance

Guide for notified bodies and manufacturers on the procedure to be followed and the documentation necessary to consult the ANSM on the quality, safety and benefit/risk profile associated with the incorporation of an ancillary medicinal substance in a medical device

Table of contents

1. Purpose and scope of application

This guide is intended for notified bodies (NB) and companies wishing to consult the National Agency for the Safety of Medicines and Health Products (Agence nationale de sécurité du médicament et des produits de santé (ANSM)) in the context of the procedure for evaluating the conformity of medical devices incorporating a medicinal substance whose action is ancillary to that of the device (AMS) for which an “authority for medicinal products” must be consulted regarding the safety and quality of the substance and the benefit/risk profile associated with the incorporation of such a substance in a medical device.

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 (hereafter designated Regulation 2017/745) in its Annex I on the general requirements regarding safety and performance (paragraph 12.1)) specifies that the quality, safety and usefulness of an ancillary medicinal substance incorporated in a medical device must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC relating to medicinal products for human use as provided for by the conformity assessment procedure described in Article 52.9 and Annex IX section 5.2 of the said regulation.

This guide concerns medical devices, including active implantable medical devices, which incorporate an ancillary medicinal substance. According to the safety and performance requirements of Regulation (EU) 2017/745, these devices must obtain a scientific opinion from one of the European competent authorities (CA) for medicinal products.

This guide does not concern devices that incorporate tissues or cells of human origin or their derivatives falling under Directive 2004/23/EC whose action is ancillary to that of the devices.

This guide explains the information required to initiate the consultation and the format in which the corresponding dossier must be supplied to the ANSM. It is updated in light of the new Regulation 2017/745 applicable since 26 May 2021.

2. Glossary

CA: Competent authority

CE: conformity of a product with the community requirements incumbent on the product manufacturer

MD: Medical device

EMA: European Medicines Agency

LoQ: List of questions

NB: Notified body

QS: Quality Safety

AMS: Ancillary medicinal substance

MDR: Medical Device Regulation (Regulation 2017/745)

TSE: Transmissible Spongiform Encephalopathies

3. Regulatory texts and guides

- 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

  https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:32017R0745&from=FR

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use;

  https://ec.europa.eu/health/sites/health/files/files/eudralex/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_fr.pdf

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH);

  https://www.ich.org/page/ich-guidelines

- MDCG 2020-12: Guidance on transitional provisions for consultations of authorities on devices incorporating a substance which may be considered a medicinal product and which has action ancillary to that of the device, as well as on devices manufactured using TSE susceptible animal tissues;

  https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020-12_guidance_transitional_provisions_en.pdf

The references below are given by way of indication, the applicant must check there are no modifications in the regulation or in the guidance/guidelines mentioned.

- EMA - Consultation procedure for ancillary medicinal substances in medical devices

  https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices/consultation-procedure-ancillary-medicinal-substances-medical-devices

- EMA Guidelines on Quality / Biologicals / Non-clinical/ Clinical efficacy and safety;

  https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines

- MEDDEV 2.1/3 rev 3: “Guidance document on “Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative”;

  https://ec.europa.eu/docsroom/documents/10328/attachments/1/translations

4. Regulatory reminder

4.1. What is a medical device that incorporates an ancillary medicinal substance?

This is any medical device that incorporates a substance, which if it were considered in isolation would be considered a medicinal product and would fall under Directive 2001/83/EC. The action of this substance must be ancillary to that of the device.

Article 1, paragraph 8, first paragraph of Regulation 2017/745 stipulates that “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.”

Notes:

- *When the device incorporates a substance derived from human blood or human plasma or a substance which, used separately, is liable to be considered a medicinal product falling exclusively within the scope of application of the Annex to regulation (EC) No. 726/2004, the notified body requests an opinion from the EMA.*
- *When the action of the substance is essential and non-ancillary to that of the device, the product is then governed by Directive 2001/83/EC or Regulation (EC) No. 726/2004 and the general requirements regarding safety and performance apply to the part that constitutes the device.*

Regulation 2017/745 specifies, in Article 52.9 and in its Annex IX section 5.2 or its Annex X section 6, the procedure for consultation of a CA by a NB for the assessment of the quality, safety, and the benefit / risk profile of an AMS incorporated in a MD.
This assessment must be carried out by reference to the methods specified in Annex 1 of Directive 2001/83/EC.

4.2. Purpose of consulting a competent authority for medicinal products

The National Agency for the Safety of Medicines and Health Products (Agence nationale de sécurité du médicament et des produits de santé - ANSM), is the CA in France for medicines for human use.
The ANSM, as the other competent authorities for medicinal products, can be consulted by the NB selected by the manufacturer or its authorised representative for an opinion on the quality, safety of the substance as well as on the benefit/risk profile associated with its incorporation in the device on condition that this substance is not considered a medicinal product constituent or a medicinal product derived from human blood or human plasma as defined in Article 1 of Directive 2001/83/EC. Indeed, in such a case, the NB can only consult the EMA.

4.3. Role of the NB and of the CA in the assessment

As part of the CE marking procedure, the manufacturer submits the technical documentation to the NB demonstrating the conformity of the MD with the requirements of Regulation 2017/745.
If the MD incorporates an AMS; the manufacturer also submits a dossier to the NB allowing assessment of the quality, safety and usefulness of the AMS. The NB evaluates the usefulness of the incorporation of the AMS in the MD. Then it retains a CA to provide a QS opinion. This is called an **initial opinion**.

Subsequently, certain changes made especially to the AMS or to the MD are the subject of a new consultation. The NB asks the CA that provided the initial opinion to update it if necessary. This is called a **complementary opinion**.

More generally, any change dealing with the quality, safety of the AMS, particularly associated with its manufacturing process, must be considered to check that it does not have a negative impact on the benefit/risk profile established previously.

The ANSM can be consulted for the initial and the complementary opinions associated with a change relating to the AMS incorporated in the MD.

For the first consultation in accordance with Regulation 2017/745, the NB can solicit any European competent authority, and if applicable not necessarily that which was consulted previously according to the MD Directives.

Note

- *In the context of the consultation for a complementary opinion by the NB of a competent authority different from that which was consulted initially, the ANSM recognises the validity of the assessments conducted previously. Nevertheless, the ANSM considers that consulting a CA different from that which conducted the initial assessment must be duly justified by exceptional circumstances (example of Brexit).*
  The consultation by the NB of the competent authority that conducted the initial assessment ensures consistency in the assessment and follow-up of a dossier.

5. ANSM consultation procedure regarding the quality, safety and benefit / risk profile associated with the incorporation of an ancillary medicinal substance in a medical device

5.1. General outline of the ANSM consultation procedure

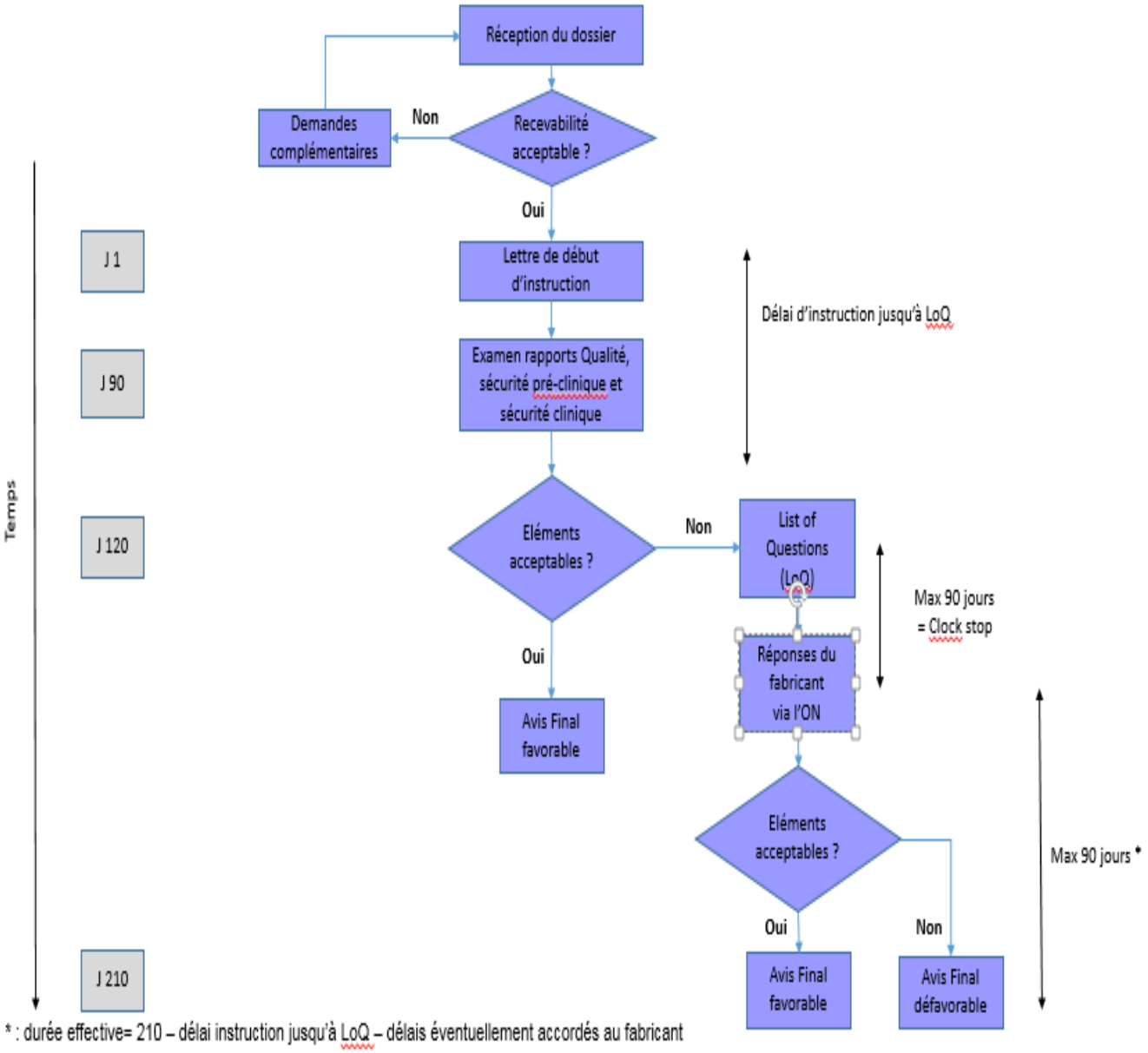
The ANSM asks NBs wishing to consult it to obtain a QS opinion to inform it of their intention 2 months before submitting the dossier.

Periodic updates are organised with the NB to evaluate the provisional dossier submission schedule.

Pre-submission meetings can also be organised, but for particular justified items requiring arbitration. In all cases the ANSM interlocutor remains the NB.

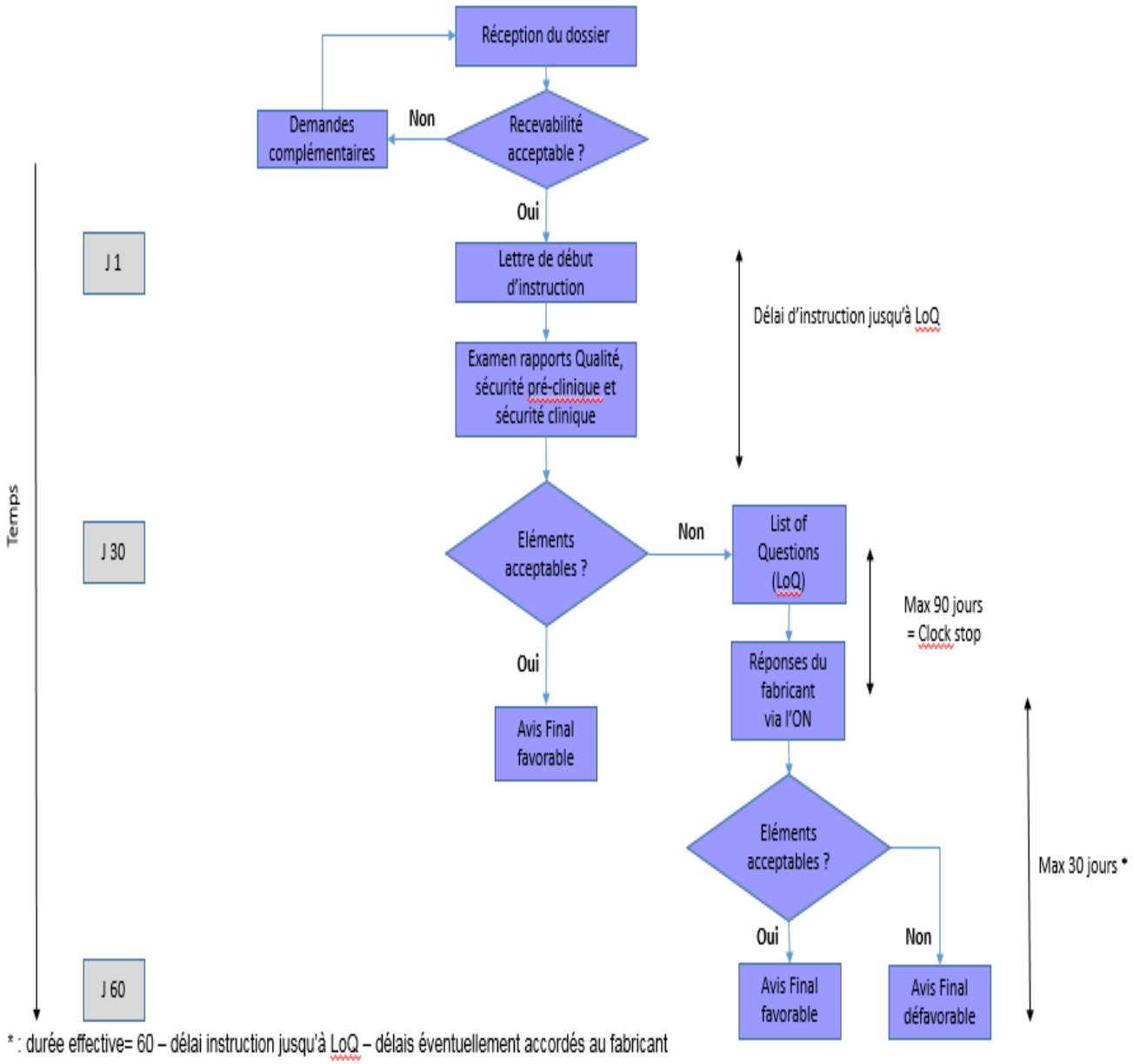
Consultations conducted within the framework of Regulation 2017/745 are considered initial assessments.

Diagram of a initial consultation procedure



* : durée effective= 210 – délai instruction jusqu'à LoQ – délais éventuellement accordés au fabricant

Diagram of a complementary consultation procedure



* : durée effective= 60 – délai instruction jusqu'à LoQ – délais éventuellement accordés au fabricant

5.2. Initial consultation application dossier

The quality, safety and usefulness of the AMS are verified by reference to the methods specified in Annex 1 of Directive 2001/83/EC.

In the context of an initial consultation, the following items are to be supplied by the NB when submitting the dossier:

- A letter of intent to apply for a QS consultation in the context of the CE marking of a class III device in accordance with rule 14 of Regulation 2017/745.
  This letter of intent must give a scientific explanation of the solely ancillary mode of action of the AMS and the main mode of action of the device.

- The “Application Form for QS consultation” (Annex 1)

- General information

  - a letter from the manufacturer authorising the transmission of documents by the NB;
  - a flow chart indicating the different sites involved in the manufacturing process of the AMS as incorporated into the device;
  - if applicable, the ISO 13485 certificates or others, of the manufacturer and the manufacturing subcontractors especially those involved in the incorporation of the medicinal substance;
  - a letter from the AMS manufacturer authorising the ANSM to access the Master Files;
  - the written undertaking of the AMS manufacturer to inform the applicant in the event that the AMS manufacturing process or specifications are modified in accordance with Annex 1 of Directive 2001/83/EC;
  - a TSE declaration and supporting documentation when the AMS is manufactured using materials of animal origin;
  - Case of consultations conducted in accordance with Regulation 2017/745 for devices already in possession of an opinion from an authority in accordance with the MD Directives. MDCG Guidance 2020-12 is applicable. The dossier to be supplied, in addition to the items expected in the context of initial assessment, must include:

    - all opinions issued previously by a competent authority;
    - a “gap analysis” of the impact on the medicinal substance of each modification made to the substance and to the device since the last opinion issued by a competent authority.

- Documentation relating to the quality of the AMS (Annex 2)

- Data relating to the safety of the AMS (Annex 2)

- The assessment report of the NB on the usefulness of the addition of the substance(s) and the corresponding clinical data.

The QS dossier must contain 5 distinct sections:

1. General administrative information, forms and other;
2. Summary of the assessment conducted by the manufacturer;
3. Documentation relating to the quality of the AMS;
4. Data relating to the safety of the AMS;
5. Clinical documentation relating to utility and favorable benefit/risk ratio associated of the incorporation of the AMS.

The different sections must be clearly identified and paginated.

Recommendations on the data to be supplied and the format of the QS dossier are specified in Annex 2 for an initial consultation application.

The dossier and its data may be presented in French or in English.

The set of documents is supplied in electronic format and on 3 USB drives.

The complete electronic dossier must be sent to the ANSM by the NB via the CESP platform.

- Choose the submission option “other submission” and not eCTD or Nees.
- In the “Comments” section, specify “MD - QS consultation”.
- Take care that the size of the zip folder does not exceed 4 Mb. If it is larger than 4 Mb, subdivide it into several subfolders.
- When submitting, send the CESP number(s) to the email address dmcdiv@ansm.sante.fr indicating in the email subject line: “MD – QS consultation”

In the event that the CESP platform cannot be accessed, the complete electronic dossier must be sent by the NB to the email address: dmcdiv@ansm.sante.fr
The subject line of this email must mention: “MD – QS consultation”

The USB drives must be sent to:

ANSM
DMCDIV
Consultation procedure for a medicinal substance added to a Medical Device
143-147 Bd Anatole France
93285 Saint Denis
FRANCE

5.3. Complementary consultation application

5.3.1. Structure of the complementary consultation application dossier

In the context of a complementary consultation, the following items are to be supplied by the NB when submitting the dossier:

- A letter of intent to apply for a QS consultation in the context of the CE marking of a class III device in accordance with rule 14 of the MDR;
  This letter of intent must give a scientific explanation of the solely ancillary mode of action of the AMS and the main mode of action of the device as well as a summary of the modifications made.

- The "Application Form for QS consultation" (Annex 1) completed up to item 17

- General information

  - a letter from the manufacturer authorising the transmission of documents by the NB;
  - a flow chart indicating the different sites involved in the manufacturing process of the AMS as incorporated into the device;
  - if applicable, the ISO 13485 certificates or others, of the manufacturer and the manufacturing subcontractors especially those involved in the incorporation of the AMS;
  - a letter from the AMS manufacturer authorising the ANSM to access the Master Files;
  - the written undertaking of the manufacturer of the AMS to inform the applicant in the event that the AMS manufacturing process or specifications are modified in accordance with Annex 1 of Directive 2001/83/EC;
  - a up-to-date TSE declaration and supporting documentation when the AMS is manufactured using materials of animal origin.

- Documentation relating to the quality of the AMS (Annex 3)

- Data relating to the safety of the AMS (Annex 3)

- An analysis of the impact of the modification on the NB assessment report on the usefulness of the addition of the AMS(s), and if there is an impact, the corresponding clinical data.

The QS dossier must contain 5 distinct sections:

1. General administrative information, forms and others;
2. Summary of the assessment conducted by the manufacturer;
3. Documentation relating to the quality of the AMS;
4. Data relating to the safety of the AMS;
5. Clinical documentation relating to utility and favorable benefit/risk ratio associated of the incorporation of the AMS.

This dossier is limited to data modified, supplemented, revised specifically in association with the modification relative to the last data items evaluated by the CA in the initial or complementary consultations, and judged relevant by the manufacturer. The absence of transmission of one of the 5 sections is to be justified by the manufacturer.

Recommendations on the data to be supplied and the format of the QS dossier are specified in Annex 3 for a complementary consultation application.
The different sections must be clearly identified and paginated.

The dossier and its data may be presented in French or in English.

The set of documents is supplied in electronic format and on 3 USB drives.

The complete electronic dossier must be sent to the ANSM by the NB via the CESP platform.

- Choose the submission option “other submission” and not eCTD or Nees.
- In the “Comments” section, specify “MD - QS consultation”.
- Take care that the size of the zip folder does not exceed 4 Mb. If it is larger than 4 Mb, subdivide it into several subfolders.
- When submitting, send the CESP number(s) to the email address: dmcdiv@ansm.sante.fr indicating in the email subject line: “MD – QS consultation”.

In the event that the CESP platform cannot be accessed, the complete electronic dossier must be sent by the NB to the email address: dmcdiv@ansm.sante.fr
The subject line of this email must mention: “MD – QS consultation”

The USB drives must be sent to:

ANSM
DMCDIV
Consultation procedure for a medicinal substance added to a Medical Device
143-147 Bd Anatole France
93285 Saint Denis
FRANCE

5.3.2. Examples of modifications that require a complementary consultation from the ANSM

By way of example, the modifications made to one or more substances incorporated in the medical device and which may require a complementary consultation from the competent authority, may be (non-exhaustive list):

- A change of AMS manufacturer
- A modification of the process for incorporating the AMS in the medical device
- A modification of the sterilisation process or the sterilisation method
- A modification in the specifications of controls relating to the characteristics of the AMS
- Any modification of the medical device that could have an impact on the availability or release of the AMS; (for example, increase in the size of the MD, modification of the surface area of the MD)
- A modification of the medical device that could have an impact on the stability of the AMS
- A change in the formulation or the grade of the AMS or of an intermediate substance
- A significant change in the manufacturing process or change in the specification of the AMS as notified by the manufacturer of the substance
- A change in the quality control tests relative to the AMS during manufacture
- Extension of the shelf life period
- A modification of the indication and of the intended use of the MD, for example: modification of the implantation site.

More generally, any modification with an impact on the quality, the safety of the AMS must be considered, to check that it does not have a negative impact on the benefit / risk profile established previously.

The ANSM will also take into consideration new data relating to the usefulness of the incorporation of the substance in the MD as was determined by the NB, so as to confirm (or not) that the quality and safety of the AMS are guaranteed and that the modifications do not have a negative impact on the benefit / risk profile established previously.

Certain modifications which do not impact the AMS directly could nevertheless have an impact on the medicinal substance (e.g. change of MD manufacturing site..). It is the responsibility of the NB to solicit or not solicit the CA and to justify its decision.

5.3.3. Examples of modifications that require an initial consultation from the ANSM

The ANSM considers that this does not involve a complementary consultation application but an initial application for a MD incorporating a medicinal substance in the case where modifications in particular concern:

- The addition of one or more new substances that could be considered a medicine if used alone
- The replacement of a substance by another substance that could be considered a medicine if used alone
- the addition of an indication to the MD
- the addition or change of an administration route.

The withdrawal of one or more substances that could be considered a medicine if used alone will be to be considered on a case-by-case basis.

If there is doubt as to whether a modification application or initial application is appropriate, the NB can request the opinion of the ANSM, especially when the modification concerns the intended purpose of the MD claimed by the manufacturer without modification of the AMS added to the device evaluated previously. For this purpose, the NB will consult the ANSM in writing (letter, email).

5.3.4. Examples of modifications that do not require a complementary consultation from the ANSM

The following cases do not require a consultation but just the simple communication of information by letter:

- Extension of the product line consisting solely in adding a brand name without substantial changes being made to the MD
- Change of the product trade name without changes being made to the product itself
- New address or new manufacturer name without change of production site, new legal entity

5.4. Admissibility of the dossier

Admissibility is determined by the ANSM within 30 days of receipt of the dossier. It consists in checking that all items necessary to the assessment of the dossier are indeed present, and that the application corresponds to the assessment of a substance with an ancillary function, falling within the sphere of competence of the ANSM.

If during the admissibility assessment, it appears that:

- The dossier is not structured, paginated in accordance with Annex 2 or 3 it will not be judged admissible
- The application does not correspond to an assessment of a substance with a function ancillary to that of the MD, falling within the sphere of competence of the ANSM, the NB will be informed that their application has been rejected
- The application is not admissible as items are missing from the dossier, the ANSM sends a letter to the NB requesting further information listing the missing items. A single letter is send in the admissibility phase
- The application is admissible, the NB will be informed that its application has been registered with the ANSM. The application number indicated in the letter must be mentioned in all subsequent correspondence.

After 30 days,

- If the dossier is not yet complete, the ANSM sends a letter indicating non-admissibility. The NB must resubmit an initial consultation application
- If the dossier is complete, the ANSM sends a letter to the NB indicating admissibility. The date of the letter determines the first day of the beginning of the ANSM assessment procedure (D1). The regulatory period defined in Regulation 2017/745 will begin from D1.

5.5. Instruction of the application

As soon as a dossier is admissible the assessment begins.

The assessment may involve the ANSM boards in charge of quality assessment, the safety of medicines, its experts and/or working groups.

Requests for clarification or additional information are expressed by the CA to the NB on D120 for an initial assessment and on D30 for a complementary assessment.
The ANSM may also propose a meeting to the NB to clarify certain points.

In case of questions (on D120 or D30), the regulatory period is stopped until a response is received from the NB. The “clock stop” is for a maximum duration of 90 days. In the absence of a response at the end of the “clock stop” the dossier is closed.

On receipt of additional information, the assessment process can then resume and the final favourable or unfavourable opinion of the ANSM will be provided within the time frames defined in regulation 2017/745 added to the time taken for the NB to respond to the questions raised.

At any time in the procedure, the NB can withdraw its application for a consultation on condition that the final opinion of the ANSM has not been issued. The NB must inform the ANSM in writing of the

withdrawal of its assessment application and specify the reason for this withdrawal. If the withdrawal is motivated by the decision to present the consultation application to another competent authority, the identity of the new CA must be specified in the withdrawal letter.

5.6. Notification of the opinion provided by the ANSM and follow-up

In taking its decision on CE marking, the NB will duly take into consideration the opinion expressed by the ANSM.
If the opinion provided by the ANSM is unfavourable, the NB cannot issue the certificate.
In all cases, the NB will inform the ANSM of its final decision using the form in Annex 4. The NB must mention the headings of the MD covered by the QS opinion and the certificate numbers in a precise and detailed manner.
The final opinion of the ANSM will be incorporated by the NB and the manufacturer in the documentation relating to the device.

6. Monitoring and updating of opinions provided

If the CA consulted obtains information on the AMS relating to the incorporation of the substance in the device, that is liable to have an impact on the quality, safety and benefit/risk profile established previously, it issues a complementary opinion to the NB.
The notified body takes this opinion into account in the conformity assessment procedure and reconsiders its assessment.
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Annex 1

Consultation on an ancillary medicinal substance integrated in a medical device

Application form for QS consultation

This application form is to be used for an application for a scientific consultation on an ancillary medicinal substance used in a medical device submitted to the ANSM in accordance with MDR 2017/745.
A combined form is acceptable for a range of strengths or concentrations of the ancillary medicinal substance and for a range of similar devices (e.g. a range of catheters made of the same material) incorporating the same medicinal substance from the same manufacturer (give information successively, where appropriate).
To be submitted to dmcdiv@ansm.sante.fr

DECLARATION and SIGNATURE

Name of device:

Ancillary medicinal substance(s)

Dosage / Concentration of medicinal substance(s)

Notified body:

Person authorised for communication on behalf of the notified body:

Applicant for device approval:

I hereby request a consultation with the ANSM concerning the medicinal substance(s) integrated in the above mentioned device. I declare that, for this product no application for consultation has been submitted to any other medicinal authority and no consultation procedure is ongoing.
It is hereby confirmed that all existing data which are relevant to the quality, safety and usefulness of the ancillary medicinal substance(s) have been supplied in the dossier and that all required headings have been filled.

On behalf of the notified body

Signature(s)

Name Function

Place and date (dd-mm-yy)

1. Name of product - Other name of the medical device
If different (Invented) names are proposed, these should be listed by identifying the member State in which they are marketed

2. Consultation reference number
(Insert number allocated by ANSM

3. Name of the ancillary medicinal substance
Note only one name should be given in the following order of priority : INN, Ph. Eur, National Pharmacopeia, common name, scientific name; the active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant

4. Type of application

4.1 Initial advice for a medical device

☐ Initial consultation on an ancillary new medicinal substance (i.e. the medicinal substance does not have a French or European marketing authorization (MA))

☐ Initial consultation on a known ancillary medicinal substance from a known source (i.e. the medicinal substance have a French or European MA for the purpose of the integration into the medical device)

☐ Other

4.2 Modification for medical device already CE marked

☐ Follow-up consultation due to a variation on an ancillary medicinal substance

☐ Follow-up consultation due to variation on the medical device

Date and reference of previous consultation procedure

5. Claims made in product information (only for initial advice)

☐ Not applicable

Please state claims as made in product information, including any additional claims relating to added substance

5.1 Claim

5.2 Additional claims

☐ none

☐ Yes:

6. Background on change to substance (Only for complementary consultation)

☐ Not applicable

6.1 initial reference number (ANSM or other CA)

6.2 Background on change
Please explain the background to proposed change in relation to substance

6.3 Impact on claims

☐ Not applicable

☐ Modifications proposed

Specify the exact current and proposed text (if changing claim)

Current claims

Current additional claims

Proposed new claims

Proposed additional new claims

7. Notified Body
(Insert name, address, telephone, e-mail and name of contact person)

8. Device manufacturer seeking device approval
(Insert name and address and contact details for person authorised for communication throughout the consultation)

9. Manufacturer of device (if different from section 8)
(Insert name and address)

☐ Not applicable

10. Manufacturer(s) of intermediate products of the active substance(s)
(Insert name, address, telephone and email. Attach flow chart)

11. Manufacturer(s) of the active substance(s)
(Insert name, address, telephone and email of each supplier)

12. Pharmacotherapeutic classification
Use ATC classification system,: WHO ATC weblink: https://www.whocc.no/atc_ddd_index/

13. Pharmacopea Eur Certificate of Suitability
(Insert reference number if applicable)

☐ Not applicable

14. Active Substance(s) Master File
(Insert reference if applicable)

☐ Not applicable

15. Description of device with ancillary medicinal substance
(Enter amount of active substance in each device, also concentration per unit volume/area as appropriate, description of device, packaging components, shelf-life details and recommended storage conditions. Specify if the medical device without the active substance is already CE marked.
A single form may be used for a group of products where the active substance is qualitatively and quantitatively identical

Description of device and intended purpose

Ancillary medicinal substance(s)	**Quantity**	**Unit**	**Reference / Monograph standards e.g. PhEur**
a.			
b.			
c.			

Packaging components and pack size

Proposed Shelf-life (unopened) **Proposed Shelf-life (in use)**

Recommended storage conditions

16. Intended purpose of the ancillary medicinal substance as incorporated into the device with scientific explanation that the action of the medicinal substance is only ancillary to that of the device.

17. Utility of the ancillary medicinal substance as incorporated into the device. Summary of Notified Body assessment

18. Checklist of data submitted to be completed only when the complete dossier is submitted

Cover letter	☐
Application form	☐
Documentation relating to the quality of the medicinal substance	☐
Documentation relating to the safety of the medicinal substance	☐
Notified Body report on usefulness of the ancillary medicinal substance and relating clinical data OR gap analysis in case of complementary consultation	☐
Letter from the manufacturer authorizing the communication of documents by the notified body	☐
Flow chart indicating the different sites involved in the manufacturing process of the ancillary medicinal substance as incorporated into the device	☐
Good Manufacturing Procedure inspection certificate / ISO 13485 certificate for manufacturing sites / others	☐
Letter(s) of authorization to access to Active Substance Master Files or copy of Ph. Eur. Certificate of Suitability	☐
Copy of written confirmation from the manufacturer of the ancillary medicinal substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex 1 of Directive 2001/83/EC as amended	☐
TSE Statement and supporting documentation where the ancillary medicinal substance is manufactured using materials of animal origin	☐

Comments:

QS DOSSIER FOR AN INITIAL CONSULTATION APPLICATION

1. Paginated table of contents of the dossier

2. General information

- Name and address of the manufacturer
- Full trade name of the medical device
- Description of the medical device
- Indication of the medical device
- Route of administration
- Identification of the ancillary substance(s):
  - name
  - concentration (in mass /mass and in mass/per unit of the MD)
- Instruction leaflet indicating contraindications, precautions for use and shelf life (before opening, in situ)
- Labelling expressly indicating the addition of an ancillary substance
- Risk management report including the risk analysis for integration of a medicinal substance in the medical device
- Curriculum vitae of experts consulted (if applicable) and demonstration of the absence of conflict of interest

3. Summary of the assessment conducted by the manufacturer

This section of the dossier includes:

- A scientific explanation of the qualification of the product as a class III device in application of rule 14 of Annex VIII of Regulation 2017/745
- A justification of the addition of an ancillary substance and of its activity (benefits of the medical device-substance combination)
- A critical summary of the conclusions drawn by the manufacturer on the basis of the data supplied, on the quality, the safety of the addition of an ancillary substance

4. Documentation relating to the quality of the ancillary substance

4.1. Conformity of the incorporated substance

4.1.1 Raw material(s) medicinal substances to be incorporated in the medical device

The items provided must contain:

- A description of the manufacturer of the medicinal substance(s);
- The source of this substance;
- Data from trials carried out to evaluate the quality of this substance;
- A European Pharmacopoeia: Certificate of Suitability (CEP);

  Failing this, a dossier such as an Active substance Master File, structured in line with CTD format, module 3.2.S (except for biological medicinal substances). This dossier includes in particular the description of the substance manufacturing process, product specification compliance data and substance stability data during storage under the conditions defined in the instruction leaflet.

- In the case of devices incorporating tissue or cells of human or animal origin or their derivatives as ancillary elements, the physical-chemical and biological characterisation and the detailed description of the production process and its control.

4.1.2 Description of the medical device with the incorporated substance(s)

- The description of the medical device - finished product - and the description of the medicinal substance(s) incorporated in each device, that is the qualitative and quantitative formulation must be supplied;
- This formulation must be accompanied by the upper and lower specification limits, the thresholds of which must be justified with regard to their safety (Directive ICH Q3B) and their efficacy;
- If the substance is modified during its incorporation in the medical device, appropriate information must be supplied;
- If the medicinal substance is degraded during its incorporation in the medical device, the degradation products or impurities must also be characterised if required in the specifications, and the associated limits duly justified with regard to their safety.

4.1.3 Description of the manufacturing process and associated controls

- A comprehensive description of the manufacturing process must be supplied. In particular, a detailed description of the section describing incorporation in the medical device must be provided;
- If the substance is modified during its incorporation in the medical device, appropriate information must be supplied;
- The submission of summaries of studies and validation protocols of manufacturing processes demonstrating that the incorporation of the substance in the device is performed in a reproducible and controlled manner, is recommended;

4.1.4 Documentation of the results of controls carried out throughout the manufacturing process

- The raw materials / medicinal substances must be described and documented with certificates of analysis demonstrating their conformity with their chemical and biological specifications. If necessary, the substance analyses must comply with the European Pharmacopoeia monographs;

- The controls implemented during manufacturing must be documented, with results that demonstrate the conformity of the medicinal substance at each stage of manufacture;

- The controls carried out on the finished product (ready to be used) must be documented, with results that demonstrate the conformity of the medicinal substance with its final specification (chemical and biological characteristics);

- Results documented in 3 validation batches are recommended, including at least one produced under routine production conditions;

Note: The validation methods used for the performance of these controls must be described and validated in an appropriate manner. Data validating these analysis methods must be supplied in the dossier.

4.2. Interactions between the medical device and the medicinal substance:

- When the substance is integrated in the medical device using an impregnation process which releases the medicinal substance over time, substance release kinetics must be supplied and discussed with regard to their efficacy and safety;

- When the substance is linked to the medical device using a grafting or coupling process, the latter must be discussed with regard to its efficacy and safety;

- Content/container interaction: products discharged from medical device materials must be identified and discussed with regard to their impact on the quality and stability of the incorporated medicinal substance.

4.3. Stability studies

- Stability studies must be deposited, demonstrating the conformity of the medicinal substance throughout the shelf life of the product. Stability storage conditions must be specified, taking account of recommendations indicated in the instruction leaflet indicating the product storage conditions (ICH Q1A R2).

  Stability data obtained in storage in accelerated and ambient conditions are expected.

- Moreover, if the conditions of use are specific to the medical device, data must be deposited demonstrating that the incorporated substance retains its properties throughout its use (example: stability in light).

5. Data relating to the safety of the ancillary substance

5.1. Preclinical data relating to biological safety

For the active medicinal substance section

- Complete paginated table of contents

- Instruction leaflet
- Summary of the non-clinical documentation (or expert report) on the preclinical safety of the active medicinal substance incorporated as an ancillary element in the medical device
- Tabulated summary of non-clinical studies (pharmacology, pharmacokinetics and toxicology)
- non-clinical documentation on the preclinical safety of the active medicinal substance incorporated as an ancillary element in the medical device, according to the requirements of section B.3 of the guideline MEDDEV 2.1/3 rev. 2 [(a), (b), (h) – (o)]
- Bibliography

For the active substance - device interaction section:

- The assay methods used must be sensitive and precise. The assay results should be reproducible (in the laboratory) and repeatable (between laboratories) and reliable. Also, all assays must be conducted according to best current laboratory/quality practices, such as for example the GLP or ISO 17025.
- The risk assessment strategy must imperatively be based on the combination product (MD + active substance).

  If applicable particular attention must be paid to assessment of the safety of discharged impurities, degradation products and contaminants.
  If equivalence is claimed a demonstration of technical, biological and clinical equivalence must be provided.
  In the case where the manufacturer decides not to carry out any assay expected in the demonstration of preclinical safety, justification for non-performance must be provided.
- Chemical characterisation: qualitative and quantitative composition of materials; description of their toxicological profile.
- Release kinetics of the active substance of the MD
- Justification of the choice of concentration of the active substance in relation to the indication and intended purpose of the MD
- For each of the biocompatibility assays including implantation studies in animals, the results are presented in the form of a complete summary per study, with version number, date and signature, reprising the following sections of the full report:

  - the dates of the beginning and end of the test,
  - the methodology used (standards, guidelines, ...), with the species or cell types studied, the number and sex of the animals in each group,
  - assay item characteristics (name, reference, batch, qualitative and quantitative description, size and number of devices assayed, sterility, ...),
  - If the assay item is different from the device to be studied in the research, the differences must be described, qualitatively and quantitatively, and a scientific justification must be provided so that these devices can be considered identical;
  - If the assay item is an extract, the type of extract will be described (solvent);
  - the modes of use of the device in the assay in question (draw a parallel with the modes of use in the clinical investigation);
  - the duration of use;
  - all observations made: by way of example, the presence of particles in an extract, death of animals (imputable to the device studied or not),...;

- the results comprising in particular the nature, intensity, time frame of appearance; duration of all the effects observed (imputable to the device to be studied or not), their reversibility, the total mortality rate and that imputable to the device to be studied;
- the conclusion(s);
- if applicable, the full reports can be requested by the ANSM.
- A critical analysis of all the results of the biocompatibility studies should be provided in a differentiated manner;
- The absence of biocompatibility assays in accordance with the recommendations of standards EN NF ISO 10993 is to be justified. The choice of biocompatibility assay strategy is also to be justified in relation to the dangers and risks identified in relation to the composition and use of the device to be studied.

♦ The full reports of studies dealing with the assessment of the biocompatibility of the combination [MD+active substance] must be attached.

5.2. Viral safety data

In the case of substances of animal origin, the dossier must contain data demonstrating viral safety. In particular control of the TSE risk must be documented.

5.3. Clinical data on the safety of the ancillary substance

Data from assays carried out to evaluate the clinical safety of the substance must take into consideration the intended purpose of the device.

The clinical documentation includes:

♦ The analysis of clinical risks;

♦ The assessment of any scientific literature demonstrating the equivalence of the MD to a comparator MD and conformity with requirements;

♦ If applicable, the results of clinical investigations dealing with the MD in question;

♦ If applicable; a combination of the 2;

♦ The analysis of the benefit/risk ratio and risk management, and in particular information on the known or foreseeable risks, adverse effects, contraindications and warnings;

♦ Detailed information on the medicinal substance or on the tissues, cells or their derivatives, and on compliance with general directions regarding safety and performance and the management of particular risks posed by the substance or by the tissues, cells or their derivatives, and evidence concerning the added value presented by the incorporation of these substances in terms of the clinical benefit and/or safety of the device;

♦ The instruction leaflet.

QS DOSSIER FOR A COMPLEMENTARY CONSULTATION APPLICATION

1. Paginated dossier table of contents

2. General administrative information

- Name and address of the manufacturer
- Full trade name of the medical device
- Description of the medical device
- Indication of the medical device
- Route of administration
- Identification of the ancillary substance(s)
    - name
    - concentration (in weight/weight and in weight/unit of MD)
- Instruction leaflet indicating contraindications, precautions for use and shelf life (before opening, in situ) identifying the modifications made
- Labelling expressly indicating the addition of an ancillary substance
- The risk management report identifying the modifications made
- Curriculum vitae of experts consulted (if applicable) and demonstration of the absence of conflict of interest

3. Summary of the assessment conducted by the manufacturer

This section of the dossier includes:

- A scientific explanation of the qualification of the product as a class III device according to rule 14 of Annex VIII of the Regulation 2017/745
- A justification of the addition of an ancillary substance and of its activity (benefits of the medical device-substance combination)
- A critical summary of the conclusions drawn by the manufacturer on the basis of the data supplied, on the quality, the safety of the addition of an ancillary substance

4. Documentation relating to the quality of the ancillary substance

The dossier must be structured as an initial consultation dossier. The structure of the dossier is unchanged but each paragraph will be completed with the wording “unchanged” if applicable and the justification of the absence of impact on this section of the dossier.

The paragraphs where modifications are made must contain complete data with an explanation of the impact of the change made to the substance or to the medical device.

For the content of this section, refer to Annex 2

5. Data relating to the safety of the ancillary substance

The dossier must be structured as an initial consultation dossier. The structure of the dossier is unchanged but each paragraph will be completed with the wording “unchanged” if applicable and the justification of the absence of impact on this part of the dossier.

The paragraphs where the modifications are made must contain:

- complete data from the preclinical experiments, post-marketing surveillance and/or the literature,
- an explanation of the impact of the change made to the substance or to the medical device.

For the content of this section, refer to Annex 2.

Annex 4

Consultation procedure for a medicinal substance added to a medical device

Notified body decision

1. Name of product	**2. Consultation reference number***(Insert number allocated by ANSM)*
3. Notified Body *(insert name, address, telephone and e-mail address of contact person)*	**4. Applicant seeking device approval** *(insert name and address)*
5. Decision of notified body	
❒ **The EC certificate was issued** ❒ **The EC certificate was not issued** *(Please comment as appropriate)*	
Signature **Date** **Capacity in which signed:**	

Please complete all boxes and return form to:
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DMCDIV – dmcdiv@ansm.sante.fr
Consultation procedure for a medicinal substance added to a Medical Device
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