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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

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I. Consultations for a substance which may be considered a medicinal product and which has action ancillary to that of the device (including human blood derivatives)

Consultation procedure under the MDD and AIMDD

According to Annex I section 7.4 of Directive 93/42/EEC on medical devices (the MDD), and Annex I section 10 of Directive 90/385/EEC on active implantable medical devices (the AIMDD), for devices containing a substance which, if used separately, would be considered to be a medicinal product and which is liable to act upon the body with an action ancillary to that of the device, the notified body is required, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, to seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMA) on the quality and safety of the substance in the medical device, including the clinical benefit/risk profile of the incorporation of the substance into the device. Similarly, where changes are made to that substance, particularly relating to its manufacturing process, the notified body is required to consult with the same authority in order to confirm that the quality and safety of that substance are maintained and to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance in the medical device. This consultation on changes is referred to as supplementary consultation in this guidance document.

There is an equivalent consultation requirement for medical devices containing a human blood derivative with ancillary action. In this case the notified body is required to consult the EMA only.

Transitioning from MDD and AIMDD to MDR

Regulation (EU) 2017/745 on medical devices (the MDR) establishes a similar requirement in Article 52 (9) (Annex IX section 5.2 and Annex X Section 6): for devices incorporating, as an integral part, a substance which, if used separately, may be considered to be a medicinal product[1] and which has an action ancillary to that of the device (hereafter referred to in this document as the ancillary substance), the notified body is required, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, to consult a medicinal products authority designated by a Member State or the EMA[2] on the quality and safety of the substance, including the benefit or risk of the incorporation of the substance into the device. The notified body is

[1] including a medicinal product derived from human blood or human plasma

[2] only the EMA in the case of medicinal products derived from human blood or human plasma, or those falling exclusively within the scope of Regulation (EC) 726/2004

required to do so both for the initial conformity assessment of the device (this consultation is referred to as initial in this guidance document) and for any subsequent changes to the ancillary substance, in particular in relation to its manufacturing process (the consultation on changes is referred to as a supplementary consultation, by analogy to the MDD/AIMDD). A competent authority designated by a Member State in accordance with Directive 2001/83/EC or the EMA (hereafter referred as medicinal products authority in this document) consulted has 210 days since the receipt of all the necessary documentation to provide its opinion in the case of an initial consultation, or 60 days for a supplementary consultation. Unlike the MDD and AIMDD, the MDR also states that the notified body may not deliver the certificate if the opinion is unfavourable (Annex IX 5.2 (e) and (f)).

This document provides guidance on fulfilling this requirement for the first time under the MDR for devices which already underwent a consultation with a medicinal products authority according to Annex I 7.4 of the MDD or Annex I 10 of the AIMDD.

Consultation for ancillary substances under the MDR for devices which have undergone the consultation under the MDD or AIMDD

In order for the notified body to issue the first certificate for a given device under the MDR, a full conformity assessment covering all requirements has to be carried out even if the device has been certified under the MDD (Q&A IV.1 MDCG 2019-6). For devices containing ancillary substances, this includes the consultation of the medicinal products authority as per Article 52 (9) of the MDR.

For some devices, there may be no change to the device, the ancillary substance and its manufacturing process since the last consultation of the medicinal products authority under the MDD/AIMDD. Nevertheless, there may be changes in the documentation of the device due to the new requirements of the MDR, for example in clinical evaluation, which have a bearing on the quality, safety or usefulness of the ancillary substance. There may also be changes in the assessment of the device and its documentation by the notified body under the MDR. Lastly, the medicinal products authority may have new information on the substance, leading to a modified or different opinion.

For the first consultation under the MDR, the notified body is required to submit the full documentation package to the medicinal products authority as described in dedicated guidance. The notified body is free to approach any medicinal products authority at its discretion, not necessarily the one consulted under the MDD/AIMDD. This should include the last opinion of the medicinal products authority under the MDD/AIMDD (whether initial or supplementary), as well as a consolidated list of changes, if any, in the following:

- the ancillary substance,
- its manufacturing process,
- the way the substance is incorporated into the device,
- design, manufacturing of the device which could influence the quality, safety or usefulness of the ancillary substance, and/or
- the parts of the technical documentation related to the above aspects.

If there were no changes to some or any of the above, the package may be accompanied by a declaration by the notified body to this effect, stating the elements that have remained identical. If there have also been no changes to the assessment of this documentation by the notified body, this may be included in the declaration. Should there be only administrative changes to the above (e.g. changes of names or addresses, changes in document layout, etc.), these should be clearly detailed in the declaration.

The medicinal products authority may consider the depth of its review given the extent of the changes since the previous consultation under the MDD/AIMDD. It is at the discretion of the medicinal

products authority to issue its opinion in less than 210 days. If many elements concerning the substance remain identical, the medicinal products authority is highly recommended to expedite its review.

The medicinal products authority may contact the authority consulted on this device under the MDD/AIMDD, who may, at its discretion, confirm the opinion provided in the previous consultation and/or share any additional information. The final opinion for the consultation under the MDR and its issuance according to the stipulated timeline remains the responsibility of the medicinal products authority to which the notified body submitted the request under the MDR.

Note on "liability to act upon the body"

It should be noted that Annex I 7.4 of the MDD refers to devices in which the substance is **liable to act upon the body**. In the MDR (Article 52(9), referring to Article 1(8), and Section 5.2 of Annex IX), this is no longer the case. Therefore, for all those devices where the "liability to act upon the body" was used by the manufacturer as a justification not to follow the consultation, the consultation must take place under the MDR. In those cases where there are doubts on the applicability of the consultation, independently of any considerations concerning the classification of the device, the notified body should seek the scientific opinion as described in Annex IX Section 5.2 (b) of the MDR.

Relevant text from MDD and MDR

MDD – Annex I Section 7.4 [emphasis added]

Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is ***liable to act upon the body*** *with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC.*

*For the substances referred to in the first paragraph, t****he notified body shall, having verified the usefulness of the substance*** *as part of the medical 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 or the European Medicines Agency (EMEA)*** *acting particularly through its committee in accordance with Regulation (EC) No 726/2004 (1)* ***on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device****. When issuing its opinion, the competent authority or the EMEA 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.*

Where a device incorporates, as an integral part, a human blood derivative, ***the notified body shall, having verified the usefulness of the substance*** *as part of the medical device and taking into account the intended purpose of the device,* ***seek a scientific opinion from the EMEA****, acting particularly through its committee,* ***on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device****. When issuing its opinion, the EMEA 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.*
Where changes are made to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority

shall take into account the data related 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 established benefit/risk profile of the addition of the substance in the medical device.

MDR – Annex IX 5.2 b

(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 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 relating to the usefulness*** *of incorporation of the substance into the device as determined by the notified body.*

II. Consultations for medical devices containing TSE susceptible animal tissue under the MDR, where such a consultation took place under the MDD or AIMDD

Article 5(4) of Regulation (EU) 722/2012 requires that for all medical devices, including active implantable medical devices, manufactured utilising tissues of animal origin which are susceptible to transmissible spongiform encephalopathy (TSE), the notified body must, through their competent authority, carry out a consultation of the other competent authorities and the Commission.

Under the MDR, this requirement remains unchanged (Annex IX Section 5.3.2).

In order to fulfil the requirements of the MDR, during the first certification under the MDR, the notified body is required to submit the full summary evaluation report as stated in Regulation (EU) 722/2012 to the competent authorities. If there have been no changes to the documentation required from the manufacturer as per Regulation (EU) 722/2012, the summary evaluation report may be accompanied by a declaration by the notified body to this effect, stating the elements that have remained identical. If there have also been no changes to the assessment of this documentation by the notified body, this may also be included in the declaration. Should there be only administrative changes to the above (e.g. changes of names or addresses, changes in document layout, etc.), these should be clearly detailed in the declaration.

As stated in Article 5(5) of Regulation (EU) 722/2012, the competent authorities and the Commission may agree on shortening the time periods for the consultation. If many elements of the summary evaluation report remain identical, it is highly recommended to expedite the review.

Relevant text from Regulation (EU) 722/2012

Article 5 (4) and (5)

4. Before issuing an EC design-examination certificate or an EC type-examination certificate, the notified bodies shall, through their competent authority, hereinafter 'coordinating competent authority', inform the competent authorities of the other Member States and the Commission of their assessment carried out pursuant to paragraph 2 by means of a summary evaluation report in accordance with Annex II to this Regulation.

5. The competent authorities of the Member States may submit comments on the summary evaluation report referred to in paragraph 4 within the following deadlines:

(a) in relation to medical devices using starting materials for which a TSE certificate of suitability as referred to in paragraph 3 has been submitted, within four weeks from the date on which the notified body informed the coordinating competent authority pursuant to paragraph 4;

(b) in relation to medical devices using starting materials for which a TSE certificate of suitability has not been submitted, within 12 weeks from the date on which the notified body informed the coordinating competent authority pursuant to paragraph 4.

The competent authorities of the Member States and the Commission may agree on shortening the time periods set out in points (a) and (b).