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Guidance on the procedural aspects for the consultation to the European Medicines Agency by a notified body on companion diagnostics

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Comments should be provided using this [template](#). The completed comments form should be sent to companiondiagnostics.consultation@ema.europa.eu.

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Executive summary

This guidance document aims to provide interested parties with appropriate guidance on procedural aspects to facilitate the consultation procedure to the European Medicines Agency by notified bodies on companion diagnostics, as per Article 48(3), (4), (7) and (8) of Regulation (EU) 2017/746 (In Vitro Diagnostic Regulation, IVDR).

A companion diagnostic is defined in Article 2(7) of Regulation (EU) 2017/746 as follows:

'companion diagnostic' means a device which is essential for the safe and effective use of a corresponding medicinal product to:

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

1. Introduction

This guidance document is intended to provide the relevant parties, in particular notified bodies, device manufacturers and medicinal product applicants, with information about procedural aspects of the consultation procedure to the European Medicines Agency by a notified body on a companion diagnostic (CDx).

In all cases, the notified body shall seek a scientific opinion on the suitability of the CDx with the concerned medicinal product(s), from either one of the competent authorities of medicinal products designated by the Member States in accordance with Directive 2001/83/EC or from the European Medicines Agency before issuing an EU technical documentation assessment certificate for the CDx.

A CDx is intended for use with (a) corresponding medicinal product(s). Depending on the type of medicinal product concerned, the notified body shall consult the European Medicines Agency or a competent authority designated by the Member States.

- In the case that the corresponding medicinal product (or one of them if multiple) falls within the mandatory scope of the centralised procedure (Annex I to Regulation (EC) No 726/2004), it is mandatory for the notified body to consult the European Medicines Agency.
- If the corresponding medicinal product is already authorised, or if an application for its authorisation has been submitted, the notified body shall consult the medicinal product authority that is responsible for the authorisation. Therefore, for a medicinal product submitted and/or authorised through the centralised procedure under the optional scope, the notified body should consult the European Medicines Agency.

In accordance with Annex IX, section 5.2, point (c) of Regulation (EU) 2017/746, the consultation will be based on the draft summary of safety and performance (SSP) and the draft instructions for use (IFU) of the CDx. According to Article 29 of the IVDR, the SSP includes, among other elements, the summary of the performance evaluation of the device. The content of the IFU is laid down in Section 20.4.1 of Annex I of the IVDR and includes, among other elements, information on a device's intended purpose and information that allows the user to be informed of any warnings, precautions, measures to be taken and limitations of use regarding the device.

2. Scope

This document gives practical guidance on what should be considered for:

- the initial consultation procedure to the European Medicines Agency by notified bodies on a companion diagnostic medical device and,
- a follow-up consultation in case of changes affecting the performance and/or the intended use and/or the suitability of the device in relation to the medicinal product(s) concerned for which the notified body considers there is a need for a supplement to the EU technical documentation assessment certificate and hence a further consultation with the European Medicines Agency.

3. Legal basis

The legal basis for the assessment of the conformity of a device by a Notified Body, as well as for the consultation procedure on CDx by notified bodies to a competent authority designated by the Member States in accordance with Directive 2001/83/EC or the European Medicines Agency is described in Article 48 of Regulation (EU) 2017/746 and in Section 5.2 of Annex IX and point (k) of Section 3 of Annex X.

For CDx, in accordance with **Annex IX, section 5.2 of Regulation (EU) 2017/746**:

(a) The manufacturer of a companion diagnostic shall lodge with the notified body an application for the assessment of the technical documentation. The notified body shall assess that application in accordance with the procedure laid down in Sections 4.1 to 4.8 of this Annex.

(b) The application shall enable the characteristics and performance of the device to be understood, and shall enable conformity with the design-related requirements of this Regulation to be assessed, in particular, with regard to the suitability of the device in relation to the medicinal product concerned.

(c) The notified body shall, before issuing an EU technical documentation assessment certificate for the companion diagnostic and on the basis of the draft summary of safety and performance and the draft instructions for use, 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 European Medicines Agency, 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, regarding the suitability of the device in relation to the medicinal product concerned. Where the medicinal product falls exclusively within the scope of the Annex to Regulation (EC) No 726/2004 of the European Parliament and of the Council (1), the notified body shall seek the opinion of the European Medicines Agency. If the medicinal product concerned is already authorised, or if an application for its authorisation has been submitted, the notified body shall consult the medicinal products authority, or the European Medicines Agency, that is responsible for the authorisation.

(d) The medicinal products authority consulted shall provide its opinion, within 60 days of receipt of all the necessary documentation. This 60-day period may be extended once for a further 60 days on justified grounds. The opinion and any possible update shall be included in the documentation of the notified body concerning the device.

(e) The notified body shall give due consideration to the scientific opinion referred to in point (d) when making its decision. The notified body shall convey its final decision to the medicinal products authority consulted. The EU technical documentation assessment certificate shall be delivered in accordance with point (e) of Section 5.1.

(f) Before changes affecting the performance and/or the intended use and/or the suitability of the device in relation to the medicinal product concerned are made, the manufacturer shall inform the notified body of the changes. The notified body shall assess the planned changes and decide whether the planned changes require a new conformity assessment in accordance with Article 48 or whether they could be addressed by means of a supplement to the EU technical documentation assessment certificate. In the latter case, the notified body shall assess the changes and seek the opinion of the medicinal products authority consulted. The medicinal products authority consulted shall give its opinion within 30 days of receipt of the all the necessary documentation regarding the changes. A supplement to the EU technical documentation assessment certificate shall be issued in accordance with point (f) of Section 5.1.

Annex X of Regulation (EU) 2017/746:

Section 3:

The notified body shall:

(k) for companion diagnostics, seek the opinion, on the basis of the draft summary of safety and performance and the draft instructions for use, of one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or the European Medicines Agency (either of which to be hereinafter referred to as 'the medicinal products authority consulted' depending on which has been consulted under this point) on the suitability of the device in relation to the medicinal product concerned. Where the medicinal product falls exclusively within the scope of the Annex of Regulation (EC) No 726/2004, the notified body shall consult the European Medicines Agency. If the medicinal product concerned is already authorised, or if an application for its authorisation has been submitted, the notified body shall consult the medicinal products competent authority, or the European Medicines Agency, that is responsible for the authorisation. The medicinal products authority consulted shall deliver its opinion within 60 days of receipt of all the necessary documentation. This 60-day period may be extended once for a further 60 days on justified grounds. The opinion of the medicinal products authority consulted and any possible update shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the opinion expressed by the medicinal products authority consulted when making its decision. It shall convey its final decision to the medicinal products authority consulted;

Section 5:

5.5. Where the changes affect the performance or the intended use of a companion diagnostic approved through the EU type-examination certificate or its suitability in relation to a medicinal product, the notified body shall consult the medicinal products competent authority that was involved in the initial consultation or the European Medicines Agency. The medicinal products authority consulted shall give its opinion, if any, within 30 days after receipt of the valid documentation regarding the changes. The approval of any change to the approved type shall take the form of a supplement to the initial EU type-examination certificate.

4. Practical recommendations

4.1. Pre-submission activities

The notified body will inform the European Medicines Agency of the start of a procedure for the evaluation of a CDx. In addition, the notified body is expected to provide an "intention to submit letter" at least 3 months before the planned date of submission. This letter should include the date of expected submission, the name of the concerned device, the device manufacturer, the classification, its intended purpose including specific medicinal product(s) related to the device, targeted indication(s) for the medicinal product(s), information about whether the submission is initial or a change and reference to parallel medicinal product(s) procedure, if applicable.

The rapporteur as appointed by the Committee for Medicinal Products for Human Use (CHMP) for the medicinal product will be the rapporteur for the CDx consultation procedure. The co-rapporteur of the medicinal product will not be involved. In case of an advanced therapy medicinal product (ATMP i.e. a medicine for human use that is classified as somatic cell therapy, gene therapy or tissue engineered medicinal product), the rapporteur will be the Committee for Advanced Therapies (CAT) rapporteur and the CHMP coordinator will be closely involved. If the consultation procedure concerns several medicinal products, one lead rapporteur will be appointed by the CHMP/CAT and the other medicinal product(s) rapporteur(s) will have an opportunity to comment on the lead rapporteur assessment report during the commenting phase, in parallel with the other CHMP/CAT members. The PRAC Rapporteur may be involved in the assessment on a case-by-case basis.

The Agency recommends early interactions with the relevant notified body, the device manufacturer, and the marketing authorisation holder(s) or applicant(s) of the medicinal product(s) (as applicable and relevant). Questions can be sent to the Agency before the expected date of submission and will be addressed in writing to assist the notified body in preparing their application. If additional guidance is needed, the notified body can request a pre-submission meeting with the rapporteur, and, as appropriate, the marketing authorisation holder(s)/applicant(s) of the medicinal product(s) (as applicable and relevant).

The section on CDx ([Medical devices | European Medicines Agency \(europa.eu\)](https://www.europa.eu/medicines)) on the European Medicines Agency website may be helpful for notified bodies when preparing the submission for a consultation procedure to the Agency.

4.2. Data requirements and format of the application dossier

Each application for consultation for a CDx shall be submitted to the European Medicines Agency using the relevant application form, that can be found on the [European Medicines Agency website](https://www.europa.eu/medicines) and containing the information described in this document.

The consultation procedure by the CHMP/CAT should focus on the suitability of the CDx for use with the concerned medicinal product(s). The aspect of "suitability" relates to the use of a CDx with (a) particular medicinal product(s), given the performance and use claimed by the manufacturer.

The aspects that are considered when assessing the suitability of a CDx for use with the concerned medicinal product(s) include the scientific rationale for biomarker selection ¹, the analytical and clinical performance, the clinical safety, and the clinical benefit to the patients (i.e. in terms of patient management and/or clinical outcome). The technical documentation dossier for the CDx, including the adequacy of the analytical method used to measure the concerned biomarker(s) and the analytical and clinical performance, will be assessed by the notified bodies as part of the conformity assessment. Therefore, as part of the consultation procedure, these aspects should only be discussed to the extent relevant for the conclusion on the suitability of the CDx for use with the medicinal product(s).

The following scenarios are envisaged in the context of the CHMP/CAT consultation procedure on the CDx:

- **Co-developed device** (to be the CDx): A device that is co-developed with a medicinal product.
- **Follow-on device** (to be the CDx): Where a medicinal product was authorised for use with a CDx, a follow-on CDx is a device that seeks the same therapeutic indication in its intended use as the original CDx. The follow-on CDx targets the same biomarker but is not developed in parallel with the clinical development programme of the medicinal product and is not necessarily based on the same technology as the original CDx. The safety and effectiveness of a follow-on CDx should therefore be highly comparable to the original CDx.

For follow-on devices, concordance/equivalence studies might need to be conducted to assess the concordance between the original and the follow-on device, particularly in case the manufacturer of a follow-on CDx device is not able to conduct a new clinical trial or to re-test patient samples from the pivotal clinical trial where the original CDx and medicinal product were evaluated.

- **Devices already marketed under Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDD)** that will qualify as a CDx under the IVDR. The two scenarios above are possible depending on how the device was initially developed.

The CHMP/CAT consultation procedure is based on the draft IFU and draft SSP as submitted by the notified body.

The application dossier should contain sufficient information about the scientific validity and/or scientific rationale for the use of the biomarker, device measurement characteristics, device development characteristics, analytical and clinical performance. For co-developed devices, it is the expectation that a summary of the results/data in the SSP and IFU will be considered sufficient taking into account that an in-depth assessment is largely performed as part of the assessment of the marketing authorisation application(s) for the concerned medicinal product(s).

For follow-on devices that are developed after marketing authorisation of the concerned medicinal product, hence no background on the development characteristics was available at the time of the medicinal product review, the notified body is advised to provide sufficient information on device

¹ According to the Biomarkers, EndpointS and other Tools ([BEST](#)) glossary, a biomarker can be defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, in-vivo Dx, or physiologic characteristics are types of biomarkers. Such biomarker or biomarkers can be present in healthy subjects and/or in patients.

For the purpose of this consultation procedure, a biomarker is considered a specific marker to (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

development characteristics in the SSP and/or IFU due to its importance for the discussion on the suitability of the device in relation to the medicinal product concerned.

Due to its importance for the conclusion on suitability of the CDx for use with the concerned medicinal product(s), a sufficient level of information about the analytical and clinical performance should be provided in the SSP and IFU. The level of information required may vary depending on the scenario (e.g. data may be summarised further when the device is co-developed and an in-depth assessment of the clinical performance has been conducted as part of the assessment of the medicinal product).

4.3. Consultation procedure to the European Medicines Agency

The applicant for the consultation procedure is the notified body in accordance with the legal provisions of Regulation (EU) 2017/746.

The CAT/CHMP assessment will follow a 60-day timetable. In case issues that prevent the adoption of a scientific opinion are identified (*i.e.* justified grounds), there is a possibility for an extension of up to a maximum of 60 days. An opinion for the consultation procedure for the CDx will be issued at the latest by the end of the extension, taking into account where applicable clarification provided by the notified body.

After the evaluation period the CHMP/EMA will issue a scientific opinion on the suitability of the device in relation to the medicinal product concerned. The CHMP opinion is sent to the notified body. In case of an ATMP, the CHMP opinion will be based on a draft CAT opinion.

The notified body will give due consideration to the opinion of the European Medicines Agency when making its decision and will convey its final decision to the Agency.

As regard to the timepoint to start the CDx consultation procedure vis a vis the medicinal product marketing authorisation or extension of indication, there is no legal requirement that the medicinal product approval and the device certification are simultaneous. For co-developed devices, early interactions between the Agency and the relevant notified body are recommended to agree on the submission date for the CDx consultation procedure.

For devices already marketed under Directive 98/79/EC which are transitioning to the IVDR and follow-on devices, the start for the CDx consultation procedure can be at any time according to CAT/CHMP timetable, as it is anticipated to be independent of a medicinal product procedure. In case the same existing test may be used for several authorised medicinal products, it is recommended to proceed with one single CDx consultation procedure.

4.4. Post-consultation phase

In accordance with point (f) of Section 5.2 of Annex IX of the IVDR, where changes are made to a CDx that affect the performance and/or the intended use and/or its suitability in relation to (a) medicinal product(s), the manufacturer must inform the notified body of the changes. The notified body must assess the changes and consult the Agency in case it identifies the need for a supplement to the EU technical documentation assessment certificate. The European Medicines Agency will give its opinion within 30 days of receipt of all the necessary documentation regarding the changes.

In case the notified body considers that a new conformity assessment under Article 48 has to be followed, a new initial consultation will be required (*i.e.* 60 days).

254 As regard to the timepoint for the start of the post-consultation procedure, it follows the same
255 principles as above.

256 **4.5. Fees**

257 The rules relating to the fees payable to the European Medicines Agency for consultations on medical
258 devices are established in Council Regulation (EC) No 297/95 and in the 'Rules for the implementation
259 of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other
260 measures'. Additional information on the applicable fees can be found on the EMA website
261 (<http://www.ema.europa.eu> – Human regulatory/ Overview/ Fees) and in the [Explanatory note on fees](#)
262 [payable to the European Medicines Agency](#).

263 Fee reductions are applicable for scientific services (e.g. consultation procedure) for medical device
264 manufacturers with SME status as registered at the European Medicines Agency SME office. For more
265 information, please refer to the '[SME user guide for micro, small and medium-sized enterprises](#)'.

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.](#)

[Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices.](#)

[Regulation \(EU\) 2017/746 of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.](#)