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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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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 (EMA) by notified bodies on companion diagnostics, as per Article 48(3), (4), (7) and (8) of Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (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 EMA by a notified body on a companion diagnostic (CDx). As per the Regulation (EU) 2017/746, a CDx is essential for defining patients' eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers (*i.e.*, biomarkers¹) identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker(s) can be present in healthy subjects and/or in patients.

As part of the conformity assessment of a CDx, 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 EMA before issuing an EU technical documentation assessment certificate or an EU type-examination certificate, or a supplement to them for the CDx.

- 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 EMA.
- 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 EMA.

¹ 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 or physiologic characteristics are types of biomarkers (Biomarkers, EndpointS and other Tools glossary ([BEST](#))).

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.

The applicant for the consultation should be a notified body duly designated to carry out conformity assessments according to the provisions of Regulation (EU) 2017/746.

2. Scope

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

- The initial consultation procedure to the EMA 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 or the initial EU type-examination certificate and hence a further consultation with the EMA.

3. Legal basis

The legal basis for the assessment of the conformity of a device by a Notified Body, including 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 EMA is described in Article 48 of Regulation (EU) 2017/746 and in Section 5.2 of Annex IX and Section 3 (point (k)) and 5.5 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 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.

For CDx, in accordance with 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

In order to facilitate the consultation procedure on companion diagnostics, in the following sub-sections EMA provides interested parties with detailed practical recommendations related to all steps of the assessment work that EMA will need to plan, conduct and deliver for a CDx consultation. The foreseen activities of the CDx consultation procedure are presented in four distinct phases, *i.e.*, the pre-submission, the submission, the assessment and, where needed, the post-consultation phase. The expected regulatory activities and the relevant documents needed per phase are described below in sections 4.1 - 4.4.

4.1. Pre-submission phase

The notified body is expected to provide an “intention-to-submit-letter” to the EMA at least 3 months before the planned submission date of request for a scientific opinion on the suitability of the CDx with the concerned medicinal product(s), using the relevant template that can be found on the [European Medicines Agency website](#). The notified body is requested to inform the EMA as soon as possible when the previously notified intended submission date for the application cannot be met, by re-sending an updated letter.

This intention to submit-letter also aims to trigger the timely appointment of the rapporteur by the Committee for Medicinal Products for Human Use (CHMP). 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. No co-rapporteur involvement is foreseen. If the consultation procedure concerns several medicinal products, one lead rapporteur will be appointed. All CHMP/CAT members will have an opportunity to comment on the (lead) rapporteur assessment report during the commenting phase. The Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur may be involved in the assessment on a case-by-case basis.

Early interactions regarding regulatory and/or procedural aspects

A product lead will be appointed by the EMA who will be the primary contact for the notified body prior to the application and throughout the procedure until the scientific opinion by the CHMP. The EMA recommends early interactions between 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 concerning timing, regulatory or procedural aspects of the CDx consultation can be sent by the notified body to the appointed product lead after receipt of the intention to submit-letter and within 2 months of the planned submission. These questions will be answered in writing by the EMA in due time. If additional guidance is needed, the notified body can request a pre-submission meeting with the product lead, the rapporteur, the device manufacturer and marketing authorisation holder(s)/applicant(s) of the medicinal product(s) (as applicable and relevant).

As regards 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. However, in a co-development scenario as described in section 4.2, early interactions between all involved parties are recommended to align the timing of both procedures, thus enabling timely access for patients to both the medicinal product and the CDx. These interactions will be of particular importance for [medicinal products reviewed under accelerated assessment](#) (*i.e.*, rapid assessment of medicines in the centralised procedure that are of

major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation) since accelerated assessment usually takes 150 evaluation days, rather than 210.

The section on CDx ([Medical devices | European Medicines Agency](#)) on the EMA website may be helpful for notified bodies when preparing the application for a consultation with the EMA.

4.2. Submission phase: application and scope

In accordance with Annex IX, section 5.2, point c) and Annex X, section 3, point k) 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 device as submitted by the notified body. According to Article 29 of the IVDR, the SSP includes, among other elements, the summary of the performance evaluation of the device. It is expected that it follows the [MDCG guidance 2022-9 - Summary of safety and performance Template](#). 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.

Each application for a scientific opinion on a CDx should be submitted to the EMA using the relevant application form that can be found on the [European Medicines Agency website](#) and containing the information described in this document. The application consists of a cover letter, application form, draft IFU and draft SSP. To facilitate the assessment, it is expected that the consultation will be started once the notified body has performed their review as part of the conformity assessment of the device and the draft SSP and IFU have been updated accordingly.

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 validity (scientific rationale) of a biomarker (*i.e.*, the association of an analyte with a clinical condition or a physiological state), the analytical performance (*i.e.*, the ability of a device to correctly detect or measure a particular analyte) and clinical performance (*i.e.*, the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user). The technical documentation dossier for the CDx, including the adequacy of the analytical method used to measure the concerned biomarker(s), scientific validity, 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 examples envisaged in the context of the CDx consultation with the EMA:

- A **co-developed CDx** is a device that is developed in a clinical development program together with the concerned medicinal product, either in view of an initial marketing authorisation or a change of the indication. This can mean that the device was developed in the framework of a pivotal clinical trial with the concerned medicinal product or of a bridging study assessing the concordance of the CDx and the device used in the pivotal clinical trial of the corresponding medicinal product. In case of a bridging study, sufficient documentation needs to be provided to conclude that the performance compares to the device used in the pivotal clinical trial of the

corresponding medicinal product and that there is no impact on clinical performance that would be incompatible with the safe and effective use of the medicinal product as described in the SmPC.

- A **follow-on CDx** is a device that seeks the same indication in its intended use as the co-developed CDx (hereafter, original CDx). The follow-on CDx targets the same biomarker but is not developed in parallel with the clinical development program of the medicinal product and is not necessarily based on the same technology as the original CDx. The analytical and clinical performance of a follow-on CDx, and the consequential safety and effectiveness of the associated medicinal product, should therefore be highly comparable to the original CDx. For follow-on devices, sufficient documentation needs to be provided to conclude that the analytical performance compares to the original CDx and that there is no impact on clinical performance that would be incompatible with the safe and effective use of the medicinal product as described in the Summary of Product Characteristics (SmPC).
- **Devices that have been already placed on the market under Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDD)** and that transition to the IVDR as a CDx. The two abovementioned scenarios apply as well depending on how the CDx was initially developed.

In case the intended purpose of a device includes several authorised medicinal products and indications, it is recommended to proceed with one single CDx consultation procedure to facilitate the assessment. All concerned medicinal products should be listed in the intention to submit-letter and in the application form.

4.3. Assessment phase: Development of scientific opinion

The EMA will provide its opinion within 60 days of the start of the procedure. 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. If further clarification is needed for the CHMP/CAT to conclude on the suitability of a CDx for use with the concerned medicinal product(s), a list of questions may be issued to be addressed by the notified body, and at their discretion with the involvement of the CDx manufacturer, within a given timeframe as part of the extension period. It is important that the Notified Body ensures that sufficient information as highlighted in section 4.2 is provided. The timetables for the CDx consultation, the start and completion dates of the procedure, as well as other interim dates and milestones, are available on the [European Medicines Agency webpage](#).

After the assessment period, and at the latest by the end of the extension, the CHMP will issue a scientific opinion on the suitability of the device in relation to the medicinal product concerned taking into account where applicable clarification provided by the notified body. In case of an ATMP, the CHMP opinion will be based on a draft CAT opinion. The CHMP opinion is sent to the notified body. The notified body will give due consideration to the opinion of the EMA when making its decision and will convey its final decision to the EMA by sending a formal notification to the product lead and rapporteur for the CDx.

4.4. Post-consultation phase

In accordance with point (f) of Section 5.2 of Annex IX and point 5.5 of Annex X 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 shall assess these changes and consult the EMA in the framework of a **follow-up consultation** in case it identifies the need for a supplement to the EU technical documentation

assessment certificate or to the initial EU type-examination certificate. The EMA will give its opinion within 30 days of the start of the procedure.

In case the notified body considers that a new conformity assessment under points (c) and (d) of Section 5.2 of Annex IX or point k) of section 3 of Annex X of the IVDR has to be followed, a new initial consultation will be required (*i.e.*, 60 days).

Notified bodies are requested to give an advance notice of their intention to submit a follow-up consultation as early as possible but at least one month prior to the planned application to the EMA. This can be achieved by means of an email to the product lead and the rapporteur that were appointed for the initial consultation, specifying the scope and the submission date of the intended application. The information is of importance for planning purposes for the EMA and the rapporteurs' assessment teams. As regards to the timepoint for the start of the post-consultation procedure, it follows the same principles as above.

4.5. Fees

The rules relating to the fees payable to the EMA for consultations on medical devices are established in Council Regulation (EC) No 297/95 and in the 'Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the EMA and other measures'. Additional information on the applicable fees can be found on the [European Medicines Agency](#) website and in the [Explanatory note on fees payable to the European Medicines Agency](#).

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

References

1. [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.](#)
2. [Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices.](#)
3. [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.](#)
4. [MDCG guidance 2022-9 - Summary of safety and performance \(SSP\) template](#)
5. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326791/> Co-published by National Institutes of Health (US), Bethesda (MD).
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