14 June 2022

Submitted comments on 'Guidance on the procedural aspects for the consultation to the European Medicines Agency by a notified body on companion diagnostics' (EMA/747623/2021)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder number	Name of organisation or individual
1	Merck Healthcare KGaA
2	EUCOPE (European Confederation of Pharmaceutical Entrepreneurs)
3	EuropaBio, Seán Byrne
4	MedTech Europe
5	EFPIA
6	Freeline Therapeutics Limited
7	MEB-CBG
8	Laboratory Corp of America Holdings (Labcorp)

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	Our comments mainly focus on the following aspects: • It is of utmost importance for European patients with unmet medical needs to have access to innovative treatments as early as possible. However, if adequate testing is not available by the time the product is approved, the access will be hampered. Especially for accelerated assessment procedures potential detrimental consequences have to be avoided if there is no simultaneous assessment of CDx and medicinal product. Scenarios for accelerating CDx review should be considered. • Ensuring adequate communication between all stakeholders during the entire process: Communication flow and responsibilities for EMA, NB and MAH/applicant of the medicinal product and CDx manufacturer need to be clearly defined. • The possibility of the medicinal product developer to directly interact with EMA is currently missing but could be very welcome to clarify questions and ensure a smooth assessment of the corresponding medicinal product. We believe the same would apply to the CDx developer. • Clarification on the transparency rules regarding EMA's opinion on the CDx would be welcome.	These comments have been noted and the Guidance has been revised accordingly. Detailed responses/outcomes are included in Section 2 "Specific comments on text". As highlighted in the procedural guidance, it is crucial and under the initiative of the NB, device manufacturer and MAH/applicant to trigger discussions with the medicines regulators in the pre-submission phase of the medicinal product application and consultation on the companion diagnostic, in particular to discuss timing of submission of both applications. It is the responsibility of the MAH/applicant and device manufacturer to involve themselves respectively in these pre-submission interactions and to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications. In the context of EMA transparency policy in conjunction with the need for establishing a procedure for a check of commercially confidential information, the Agency is investigating the possibility to publish the CHMP assessment report on the CDx consultation in due course.

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1	We would also like to stress to the Agency the importance of providing additional guidance on various content/science-related aspects. Examples include • Joint Scientific Advice opportunities with NBs • Clarifications on requirements for concordance/equivalence studies for follow-on CDx • Prorequirements for the medicinal product and associated CDx Details on aspects considered when assessing the suitability of a CDx for use with the concerned medicinal product(s) (which aspects and how will they be assessed)	These comments have been noted. It will be considered whether additional guidance is needed based on experience and knowledge gained from the initial consultations for companion diagnostics to the EMA.
2	While we appreciate this guideline, industry would benefit from further guidelines regarding the critical impact the IVD Regulation (IVDR) will have in the short term on the development of therapeutics that require a companion diagnostic (CDx). Specifically, companies that are currently planning clinical trials have no guidance as to: • what are the requirements for a performance evaluation (PE) application by the CDx partner (e.g. expected content); • how to submit such PE application, as EUDAMED is not operational; • what level of analytical validation (e.g. which studies, number of samples, etc.) is expected to be complete prior to submitting a PE application; • the timeline for review of a PE application for the proposed CDx. This is causing current challenges in planning for and executing clinical trials in Europe. There is a pressing need for guidance on performance evaluation applications and timeline for the review of these, to ensure development programs are not delayed by the current lack of clarity.	These comments have been noted. However, the MDCG would be in a better position to address the request for guidance regarding requirements for a performance evaluation (PE) application, submission of a PE application, the level of analytical validation and the timeline for review of a PE application as this falls outside the scope of the CDx consultation to the Agency.
3	EuropaBio welcomes the guidance to outline the procedure for interactions between notified bodies (NB) and EMA during CDx development.	This comment is noted.

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3	The guidance covers EMA consultation by NB. CDx may be developed for products falling outside the mandatory scope of the centralised procedure. As NB may also consult national competent authorities (NCAs) a common procedure across the EMRN would be useful.	The NCAs have been kept aware of the development of this EMA guidance through the CMDh.
3	The guidance indicates a CDx is intended for use with a corresponding medicinal product. As the use of CDx in clinical trials is considered "placing on the market", it would be useful to address the scenario where a CDx is available for use in a clinical trial and that "medicinal product" can also include "investigational medicinal product".	The current guidance specifically focuses on the consultation to the EMA regarding the suitability of the device for use with the medicinal product as part of the conformity assessment by the notified body in view of granting a certificate. The MDCG has published a Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746.
3	Early interactions between EMA, NB, device manufacturers and MAH will be important for co-development. EMA indicates written responses would be provided in the first instance with the possibility of NB requesting a presubmission meeting if necessary. The possibility to include NB and device manufacturers in medicinal product presubmission meetings to discuss CDx supporting data and timings of the EMA CDx opinion versus MAA review should be considered and could facilitate concurrent medicinal product approval and CDx availability.	As highlighted in the procedural guidance, it is crucial and under the initiative of the NB, device manufacturer and MAH/applicant to trigger discussions with the medicines regulators in the pre-submission phase of the medicinal product application and consultation on the companion diagnostic, in particular to discuss timing of submission of both applications. It is the responsibility of the MAH/applicant and device manufacturer to involve themselves respectively in these pre-submission interactions and to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications.
3	The guidance assumes co-developed CDx will only be submitted to NB at the same time as MAA for medicinal product. With potentially different review timings for CDx by NB and for MAAs by EMA, the CDx and MAA submissions may not be concurrent. To remove a CDx from the critical path for a medicinal product launch, a CDx could be	While there is no legal requirement that the medicinal product approval and the device certification are simultaneous, in order to conclude on the suitability of the CDx with the medicinal product, it is

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	submitted to NB prior to EMA submission. It would be useful for the guidance to address this scenario.	anticipated that the CHMP would also need to have reviewed the medicinal product application.
3	Consideration should be given to an accelerated timeframe for EMA opinion on CDx for medicinal products accepted for accelerated assessment eg. 30+30 days.	These comments have been noted and the Guidance has been revised. Detailed responses/outcomes are included in Section 2 "Specific comments on text".
3	The guidance notes there is no legal requirements that the medicinal product and device certification are simultaneous regarding the medicinal product authorisation. Similar legal position should be provided regarding CDx certification. NBs have outlined a rate limiting element of the IVDR that until such time as a positive opinion for medicinal product is provided the CDx cannot be considered scientifically valid. This should be clarified as the IVDR requires scientific opinion on the use of the device for its intended purpose, and this does not refer to a positive opinion on the medicinal product by CHMP.	While there is no legal requirement that the medicinal product approval and the device certification are simultaneous, in order to conclude on the suitability of the CDx with the medicinal product, it is anticipated that the CHMP would also need to have reviewed the medicinal product application.
3	NB will give consideration to EMA opinion. It would be helpful for MDCG to collaborate with NB to define a timeframe for CDx availability post receiving EMA opinion.	This comment is noted. However, the MDCG and/or NBs would be in a better position to address this request.
3	If a CDx is required for safe and efficacious use of a medicinal product, EMA's scientific assessment of the CDx should be part of the initial MAA review of the medicinal product. Consideration should be given to including the data provided to NB to support IFU and SSP also in the MAA for the medicinal product to enable EMA review of the medicinal product. This could also expedite provision of the EMA scientific opinion for the CDx when requested by the NB.	The IVDR has set out responsibilities for the NB to perform the conformity assessment of the CDx, hence duplication of data submission and review should be avoided, unless some data are considered necessary for the medicines regulators to conclude on the B/R balance of the medicinal product.
3	Context for legal position on NB (whether a CDx was be certified pre MA approval) - clarify this would be needed from the EC as not EMA remit.	*This comment is not understood.*
3	Many CDx have their label expanded beyond the initial certification eg. to cover use with a different medicinal product. It would be helpful to	This scenario was added to the Guidance.

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	address this scenario as the data requirements for a bridged CDx may differ from a new CDx.	
4	This guidance document is critical for allowing scientific opinion work of the EMA to start and interactions between Notified Bodies and EMA to run smoothly. In making its comments, MedTech Europe therefore is keen not to slow down publication of the guidance document. We hope that necessary and appropriate changes can swiftly be made so that its publication can occur soon. Nice-to-haves like visuals and flowcharts would greatly enhance this document however could be added to a next version if it is not practical to include them swiftly.	This comment is noted.
4	It would be helpful to develop MDCG/EMA Guidance on SSP for companion diagnostics.	The MDCG has published a guidance on the Summary of safety and performance Template (2022-9) in May 2022.
5	EFPIA appreciates the opportunity to provide feedback and that this important guidance document will soon become available. EFPIA would like to reiterate the following comments as particularly important: - We strongly feel that the marketing authorisation holder (MAH)/applicant for the medicinal product should be involved in the communication in every stage of the process, including the pre-submission meeting. It would therefore be useful to have more information for the medicinal product and manufacturer of the Companion Diagnostic (CDx) such as the communication flow and steps to be taken from EMA to Notified Body(NB) to CDx manufacturer to medicinal product applicant/MAH and the timeframes. - EMA and NBs should take every effort to ensure availability of the CDx at the time of approval of the medicinal product. We strongly	The CDx consultation is a stand-alone procedure initiated by the notified body to the EMA. It is not the remit of the EMA to actively inform or involve the MAHs and applicants of medicinal products in this process. The EMA and notified bodies will aim to avoid any delays in device certification or medicinal product approval where the application procedures are running in parallel. Of note, no eligibility step for the CDx is foreseen, nor call for rapporteurship as it is foreseen that the medicinal product rapporteur will also be rapporteur for the CDx. However, it is the responsibility of the CDx manufacturer and medicinal product MAH/applicant to interact early with both the notified body and the EMA to ensure timely access to treatments for patients with unmet medical needs. It

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	urge that EMA/National Competent Authorities and NB adopt a flexible interactive approach to medicinal product/companion diagnostic review to allow for acceleration in cases where it is warranted (e.g. in case of accelerated assessment). Such flexibility should take into account (i) automatic eligibility for acceleration for CDx where warranted, (ii) early and frequent access with reviewers, (iii) access to rapid clinical study and development advice, (iv) support for obtaining data in the post-market rather than premarket setting and (v) priority registrational review. - In general, given this type of consultation on CDx is new and experience on review of CDxs by medicinal product regulatory authorities may be limited, it will be important for regulatory authorities (including EMA) to set up processes and internal guidelines to streamline and harmonize the approaches taken by assessors for the consultation on CDx, to ultimately secure transparency in the process and consistent outcomes. - We also are of the opinion that the guidance should provide more details and clarity on how different views of EMA and NB during review and potential discrepant opinions will be resolved/handled in relation to the CDx approval. An easy process should be defined for follow-on devices to a co-developed device certified under the in vitro diagnostics directive, allowing the EMA CDx consultation procedure to proceed based on cross-reference to the original device data.	is the responsibility of the MAH/applicant and device manufacturer to coordinate sharing of information about their respective applications and keep each other informed on steps of their application. It will be considered whether additional guidance is needed based on experience and knowledge gained from the initial consultations for companion diagnostics to the EMA.
5	One area that stills seems ambiguous from this guidance is the expectation around the clearance needed to use a potential CDx in a clinical study. The guidance states that analytical and clinical performance data should be included in a submission, but the clinical performance data would come from use in a clinical trial. The requirements for use of a potential CDx in a clinical trial setting, and	This consultation takes place in the context of the certification of the device by the notified body and is not linked with the approval of the clinical trial in which the device might be used. The MDCG has published a Q&A on the interface between Regulation (EU) 536/2014 on clinical trials

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	any submissions or consultations needed to enable that, can be difficult to ascertain.	for medicinal products for human use (CTR) and Regulation (EU) 2017/746.
5	While we appreciate this guideline, pharmaceutical industry would benefit from further guidelines regarding the critical impact the IVDR will have in the short term on the development of therapeutics that require a CDx. Specifically, member companies that are currently planning clinical trials have no guidance as to: - What are the requirements for a performance evaluation (PE) application by the CDx partner (e.g. expected content); - How to submit such PE application, as EUDAMED is not operational; - What level of analytical validation (e.g. which studies, number of samples, etc.) is expected to be complete prior to submitting a PE application; - The timeline for review of a PE application for the proposed CDx; In addition, guidances are lacking on the following general aspects; - Guidance on how companies could seek joint voluntary scientific advice with EMA and NB on the path to medicinal product/companion diagnostic co-development, submission and approval; - How will the labelling of the medicinal product and CDx be co-ordinated and what information will be included in the respective labels of the medicinal product and CDx; - Whether labelling for already approved medicinal products with a biomarker-testing requirement (so-called CDx therapies) will need to change upon approval of CE-marked devices under the IVDR; - Additional guidance on which kind of "concordance/equivalence studies" would be required to show interchangeability between assays and how they are to be assessed for: a) clinical	These comments have been noted. However, the MDCG would be in a better position to address the request for guidance regarding requirements for a performance evaluation (PE) application, submission of a PE application, the level of analytical validation and the timeline for review of a PE application as this falls outside the scope of the CDx consultation to the Agency. It will be considered whether additional guidance is needed based on experience and knowledge gained from the initial consultations for companion diagnostics to the EMA. This consultation takes place in the context of the certification of the device by the notified body and is not linked with the approval of the clinical trial in which the device might be used, and therefore is not included in the CTIS. Moreover, in-house test for selecting patients for medicines does not fall within the certification requirement for CDx.

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	performance, b) clinical safety, c) clinical benefit to the patients, also addressing alternative scenarios in case such studies do not need to be conducted; - Guidance on the assessment of an in-house test for selecting patients for medicines e.g. there is no CE-marked CDx and therefore no NB involved. For example, for rare disease cases there may only be one lab doing in-house testing for EU; - From a practical perspective, for CDx to be used in clinical trial, will the Agency have access to the EUDAMED system? Are there plans to interconnect the CTIS (EMA system for CTs) and the EUDAMED systems in future?	
5	Finally, the guideline could benefit from a number of editorial suggestions: - We propose to include a glossary; - Line 45-56: The bullet points are essentially a duplicate of the text in the paragraph above and could be replaced by a sentence 'the NB should consult the same Agency as the medicinal product'; - Line 115: **For CDx, in accordance with** Annex X of Regulation (EU) 2017/746; - Line 245 and 254: please replace Post-consultation by **post-approval consultation** (phase/procedure); - Repetitive text in lines 180-184 and 206-211 could be removed.	Partly accepted. A glossary was not included but terms were brought in line with terminology from the IVDR. Repetitive text has been removed from the Guidance as much as possible. 'Post-consultation' was replaced by 'follow-up consultation' to enable consistent wording throughout the document.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
105 - 109	2	Comment: Manufacturers should be able to propose (and justify with appropriate evidence) whether a change does actually impact the intended use or suitability of the device for use with the medicinal product. Even if the Notified Body makes the final determination as to whether a new conformity assessment or supplement to the technical documentation is required, the manufacturer should be able to present its view. Proposed change: *(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 and provide the manufacturer's assessment, with appropriate justification and evidence, as to whether the change requires a new conformity assessment or supplement to the technical documentation. 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.*	This step is not in the remit of the medicines regulators.
111	4	Comment: delete "the"	Accepted.

		Proposed change (if any): The medicinal products authority consulted shall give its opinion within 30 days of receipt of all the necessary documentation regarding the changes.	
132 - 134	8	Comment: What is the total time required for NB review including CA or EMA consultation and final conformity assessment? Proposed change (if any): The total time required for NB review including CA/EMA consultation, and obtaining a final conformity assessment is 210 days alongside the CHMP scientific opinion. Having anticipated timelines for device manufacturers allows for better planning and coordination with the NB to ensure devices are CE marked and available to patients in a timely manner. Ensuring approval of the CDx device and drug at the same time makes the most sense as both components are required for treatment of patients.	Not accepted. Timelines of the overall conformity assessment is not in the remit of the medicines regulators. This Guidance document focuses on the procedural aspects of the consultation to the European Medicines Agency by a notified body on a CDx in accordance with timelines set out in the IVDR for the consultation.
144	4	**Comment:** 4.1 Pre-Submission activities – this section seems to create confusion with the reader as to what is in scope. **Proposed change:** please clarify in this document, if Pre-Submission activities (i.e. early interactions) are completely distinct from the actual "consultation for obtaining scientific opinion by EMA/NCA." If true that this is Pre-Submission, consider giving it a separate section. If this is for true consultation (as described in the Scope), then suggest staying consistent with terminology as defined in IVDR.	Accepted. Clarification about the purpose and timing of the pre-submission activities was added to the Guidance document and the subtitles were revised.
144, 147 and 172	4	**Comment:** the terms used in 4.1 and 4.2 don't match up. 4.1 refers only to the 'submission' whereas 4.2 refers only to the 'application'. This causes confusion for the reader, especially where the text talks of an 'intent to submit letter'. Please provide a clear link between the concepts.	Accepted. The guidance was updated accordingly.

		Will a confirmation number or some other communication be sent by EMA to indicate that the submission is complete and the procedure involving CHMP and or CAT will begin? **Proposed change:** In line 147, "…before the planned date of submission of the application." In line 147, "The letter should include the date of expected submission of the application…"	
145	1	*"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"* Comment: It is appreciated that EMA encourages early interaction between the NB, the device manufacturer and the MAH/applicant for the medicinal product but the recommended procedure is not clear. Clarification is needed regarding the scope and timelines of communication from CDx manufacturer/MAH to the NB that will enable timely submission of the "Intention to submit Letter" from NB to EMA. Will there be a separate guidance covering this topic? Clear timelines will be essential to ensure smooth assessment procedures for medicinal products and their associated CDx.	The guidance was updated to clarify that the intention to submit-letter from the Notified Body is the main mechanism to notify the Agency about an upcoming CDx consultation.
145	4	**Comment:** Should this be either EMA or NCA as per (Regulation (EU) 2017/746 Article 48(3) and Article 48 (4)? **Proposed change:** The notified body will inform either the European Medicines Agency or NCA of the start of a procedure for the evaluation of a CDx.	Partly accepted. The scope of the current Guidance is to provide practical guidance on the consultation procedure to the **European Medicines Agency** as described under "2. Scope".

		Clarification requested: Is this for consultation and not for scientific opinion which is what Article 48 indicates? Line 48 aligns with comment provided above.	The Guidance was revised to clarify that the notified body is expected to provide an "intention to submit-letter" to the European Medicines Agency at least 3 months before the planned date of the application for a request for **a scientific opinion on the suitability of the CDx with the concerned medicinal product(s)** […]
145	5	Comment (general): The MAH/applicant for the medicinal product should be involved in the communication where possible, in addition to the CDx manufacturer. Particularly in a co-development situation, it is critical that the manufacturer of the CDx is aware of the timeline for presubmission and the consultation. The CDx manufacturer may have legal obligations (via contract) to keep the medicinal product manufacturer aware of the timeline for the CDx review. Proposed change (if any): Please ensure that communication by the NB and EMA with the CDx manufacturer and manufacturer of the medicinal product is part of this process and identify the related responsibilities.	The CDx consultation is a stand-alone procedure focused on the suitability of the device for use with a medicinal product initiated by the notified body to the EMA. It is not in the remit of the EMA to actively inform or involve the device manufacturer or the MAHs and applicants of medicinal products in this process. It is the responsibility of the MAH/applicant and device manufacturer to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications. Any communication about the timeline for submission of the application would need to be discussed and agreed between the relevant notified body, the CDx manufacturer and, if applicable, the MAH/applicant for the medicinal product.
145	6	Please consider stating that the EMA consultation procedure is not conducted in parallel with the notified body conformity assessment, but instead forms part of this process, and is conducted once the notified body is satisfied that the submitted information meets conformity	Partly accepted. It was clarified that the CDx consultation to medicinal product authorities forms part of the conformity assessment by the notified body.

		assessment requirements. This would assist relevant parties, in particular device manufacturers and medicinal product applicants, in understanding the stage of CDx conformity assessment at which the EMA consultation procedure should occur.	Please consider that the IVDR does not specify that a notified body should have reached a certain stage in their conformity assessment review prior to the CDx consultation. However, it was clarified in the Guidance that to facilitate the assessment, it is expected that the consultation will only 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.
145 - 146	6	Comment: It is not clear whether the notified body notification required at the start of a procedure for the evaluation of a CDx (line 145) differs to the "intention to submit letter" required in line 146. If these are two separate notifications, please consider clarifying the mechanism for the notified body to inform the EMA at the start of a procedure for the evaluation of a CDx.	The guidance was updated to clarify that the intention to submit-letter is the main mechanism to notify the Agency about an upcoming CDx consultation.
145 - 151	8	Comment: Is the device manufacturer required to submit the completed technical file to the notified body in order for them to complete the "intention to submit letter"? If yes, how many months in advance should the sponsor/manufacturer submit the completed Technical file to the NB, in order for the NB to submit the "intent to submit letter to EMA", and meet EMA's deadline for submission of application for consultation for CDx for a specific month? For example, in order to meet EMA's initial submission assessment timeline for May 2022, as outlined in EMA's CDx Initial Consultation timetable for ATMP	The template with the required information for an "intention to submit letter" will be published on the EMA website. The timing and completeness of the technical file prior to the submission of an "intention to submit letter" to the EMA should be discussed and agreed with the relevant notified body who will be the applicant and contact person for the CDx consultation to the Agency.

		https://www.ema.europa.eu/en/documents/other/timetable-companion-diagnostic-initial-consultation-atmp_en.pdf (Deadline for Submission of CDx application is 06/05/2022), when is the latest that the Sponsor/Manufacturer should submit the completed technical file to the NB? Proposed change (if any): "The device manufacture is not required to submit the complete technical file to the NB in order for the NB to initiate an "intention to submit letter" to EMA. The Notified Body and Sponsor will have agreed to a submission date during the contracting process and based on the information provided during that time the NB will know when to provide EMA the "intent to submit letter." ". The purpose is to clarify the requirements for manufacturers to support the NB in their submission of the "intent to submit letter", and the timeline required by NB for review of technical document, in order to complete the intention to submit letter to the EMA. Having clear requirements for device manufacturers allows for better planning and coordination with the NB to ensure devices are CE marked and available to patients in a timely manner.	
146 - 147	2	Comment: The document does not describe how and when a manufacturer will be notified or involved in the pre-submission activities. Particularly in a co-development situation, it is critical that the manufacturer of the CDx is aware of the timeline for presubmission and the consultation. The CDx manufacturer may have legal obligations (via contract) to keep the medicinal product MAH/applicant aware of the timeline for the CDx review. Additionally, certainty of timelines is necessary for the CDx	The comment is noted, however, the involvement of the manufacturer of the CDx in the pre-submission phase should be discussed and agreed with the relevant notified body who will be the applicant and contact person for the consultation on a CDx to the Agency.

		manufacturer and the medicinal product manufacturer to plan potential launch activities. Proposed change: 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. The notified body will notify the CDx manufacturer when this intention to submit letter has been provided to the European Medicines Agency.	
146 - 147; 166	4	**Comment:** Is the intent to submit letter within 3 months prior to the submission date separate from the request for a pre-submission? How early can a request be initiated for a pre-submission meeting?	Pre-submission queries can be sent to the Agency after receipt of the intention to submit letter and before the expected date of submission and will be addressed in writing by the Agency to assist the notified body in preparing their application. If additional guidance is needed regarding administrative or procedural aspects of the CDx consultation, the notified body can request a pre-submission meeting with the EMA, the rapporteur, and, as appropriate, the device manufacturer and marketing authorisation holder(s)/applicant(s) of the medicinal product(s) (as applicable and relevant).
146 - 147	5	Comment (general): In addition, the NB is expected to provide an "intention to submit letter" at least 3 months before the planned date of submission. This may be difficult in some cases especially when the need for a CDx is identified late in the process e.g. as part of EMA feedback. It needs to	Not accepted. The submission of the "intention to submit letter" at least 3 months before the planned date of submission is required for planning purposes and rapporteur appointment.

		be ensured that the 3 months are not understood as a requirement which will lead to delays in the assessment of a medicinal product. Proposed change (if any): Please add at the end of the paragraph: '…., if applicable. **In cases where need for a CDx is identified late in the process, the 'intention to submit letter' should be submitted a.s.a.p, but may not be 3 months prior to the consultation application to EMA. NBs intending to do this should communicate directly with the Agency.'**	To avoid such late identified need for a CDx, it is crucial that the MAH/applicant consider scientific advice on their programme development for the medicinal product and engage early with the medicines regulators in the pre-submission phase in light of the clinical data.
147	3	Comment: Medicinal product and CDx development will involve multiple submissions to different bodies by different players. Suggest to ensure the submissions are clearly referenced. Proposed change (if any): In addition, the notified body is expected to provide an "intention to submit letter" at least 3 months before the planned date of submission **of the NB request for EMA opinion**	Accepted but slightly rephrased.
147	4	**Comment**: There is no legal basis in the IVDR for an obligation to provide an 'intention to submit letter' at least 3 months before the planned date of submission. MedTech Europe accepts that such a process may improve the timely delivery of a scientific opinion of the EMA and support Notified Bodies in having an aligned approach. However, we note that such a procedure should not *increase* the time-to-certify.	While it is recognized that there is no legal basis in the IVDR for an obligation to provide an 'intention to submit letter' at least 3 months before the planned date of submission, this is a useful means for Rapporteur appointment and planning purposes to ensure an efficient and timely assessment of the suitability of the CDx for use with the concerned medicinal product(s) by the CHMP/CAT.
147	4	**Comment:** Please clarify that "date of expected submission" is non-binding and for planning purposes only. When the NB will be ready to submit may depend on the file.	Partly accepted. Clarification was added to the Guidance that the notified body is requested to notify the European Medicines Agency as soon as possible when the

		Proposed change: This letter should include the (non-binding) date of expected submission, the name of the concerned device, …	previously notified submission date cannot be met.
148	4	**Comment:** It is unclear what is mean by providing "the classification". Since the consultation is only required for companion diagnostic devices, classification will be rule 3(f) according to IVDR Annex VIII. Might this be referring to the "type of development" (co-developed vs. follow-on device) as specified in the application form provided for the NB? **Proposed change:** Clarify what is meant by "classification" or remove it from the list of information to be provided. Proposed change: "..., device classification per Annex VIII,..."	Accepted. This wording was removed and a template for the "intention to submit-letter" will be published on the EMA website.
150 - 151	4	**Comment:** What is meant by "reference to parallel medicinal product(s) procedure"? Does this refer to a situation where the medicinal product is undergoing review by the relevant EMA committee within the same timeframe as the companion diagnostic? The NB application form references: "authorisation number/EMA procedure number (if available)". Is this intended to refer to ongoing application number in case of co-development? Or is this request simply for the static product reference number for the medicinal product? The guidance and the application form do not currently align. **Proposed change:**	Accepted. This wording was removed and a template for the "intention to submit-letter" will be published on the EMA webpage.

		Please clarify what is meant by "reference to parallel medicinal product(s) procedure". Please also clarify which reference number is requested. Guidance and application form should align here.	
152 - 161	5	Comment (general): The rapporteur as appointed by CHMP for the medicinal product will be the rapporteur for the CDx consultation. In addition the guidance states that a single consultation procedure should be used for several authorized medicinal products. Proposed change (if any): Please clarify how multiple CDx applications are bundled in one consultation process and describe what would be the criteria to appoint a lead rapporteur for the process if multiple medicinal products are concerned. Please explicitly include how adequate communication will be ensured with all MAHs / medicinal product developers during the process, particularly in case of procedures concerning several medicinal products (e.g. Next Generation Sequencing) and only one EMA lead rapporteur for CDx assessment.	Accepted. The guidance was revised to clarify that in case the intended purpose of a device includes several authorised medicinal products and therapeutic 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. A request for expression of interest will be sent to the Rapporteurs of all concerned medicinal products. The CHMP chair will appoint the lead Rapporteur based on objective criteria and expertise. The CDx consultation is a stand-alone procedure initiated by the notified body to the EMA. It is not in the remit of the EMA to actively inform or involve the MAHs and applicants of medicinal products in this process.
153 - 154	7	Comment: The Co-rap of the medicinal product will be involved similar to a regular concerned member state, however will not provide a Co-Rap assessment report. The way it is currently states, it might be confusing.	Accepted. Clarification was added to the guidance.

		Further clarification on the role of the concerned member states to be included.	
157	1	*"If the consultation procedure concerns several medicinal products, one lead rapporteur will be appointed by the CHMP/CAT..."* Comment: Adequate communication is needed with all MAHs / drug developers during the process, particularly in case of procedures concerning several medicinal products (e.g. Next Generation Sequencing), in light of the fact that there will be only one EMA lead rapporteur for CDx assessment. Proposed change (if any): We propose to establish an early and adequate information flow by NBs & EMA to all MAHs / drug developers involved in the CDx consultation. Confidentiality of information shared with different MAHs/drug developers needs to be ensured.	Not accepted. The CDx consultation is a stand-alone procedure initiated by the notified body to the EMA. It is not in the remit of the EMA to actively inform or involve the MAHs and applicants of medicinal products in this process. It is the responsibility of the MAH/applicant and device manufacturer to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications.
160 - 161	3	Comment: The wording around potential PRAC involvement is vague. We are not requesting every scenario to be included in the document, but there must have been certain settings envisaged by the EMA that triggered this sentence to be included. It would be helpful if these could be introduced into the guidance as they would be very helpful information. Proposed change (if any): The PRAC Rapporteur may be involved in the assessment on a case-by-case basis, **scenarios which may require PRAC involvement may include… LIST SCENARIOS HERE**.	Not accepted. Based on experience gained from the initial consultations, it will be explored in which specific scenarios PRAC involvement is considered relevant.
160	4	**Proposed change:** Define and/or spell out 'PRAC'.	Accepted.
160 - 161	5	Comment (technical):	Not accepted. Based on experience gained from the initial consultations, it will be

		The wording around potential PRAC involvement is vague. It would be helpful if examples could be provided of scenarios that would trigger PRAC involvement. Proposed change (if any): The PRAC Rapporteur may be involved in the assessment on a case-by-case basis, ***scenarios which may require PRAC involvement may include… <please list scenarios here>.***	explored in which specific scenarios PRAC involvement is considered relevant.
162 - 168	1	*"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)."* Proposed change (if any): As data owner and within the scope of an expected application, the CDx manufacturer should also directly be able to address approval related questions to EMA to prepare relevant documentation (SSP and IFU), in alignment with NB and MAH/applicant. Comment: We appreciate that a pre-submission meeting initiated by NBs is included in the scope of this guidance. However, similarly, the procedure for pre-submission meeting in case MAH / applicant of the	Not accepted. The IVDR foresees that this applicant is the Notified Body who is expected to keep informed the device manufacturer and involve them as needed. It is the responsibility of the MAH/applicant and device manufacturer to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications.

		medicinal product or CDx manufacturer need guidance on submission-related topics or CDx regulatory strategy should be included. Proposed change (if any): "If additional guidance is needed, the notified body can request a pre-submission meeting with the rapporteur. The marketing authorisation holder(s)/applicant(s) of the medicinal product(s) and the CDx manufacturer should be informed and have the option to participate."	
162 - 167	2	Comment: We agree with the suggestion for early interactions between the notified body, the device manufacturer, the medicinal product MAH/applicant, and the EMA. However, the pre-submission activities as described do not require inclusion of the CDx manufacturer. Rather, the Notified Body has discretion as to whether to seek input from EMA on questions, or whether to seek a pre-submission meeting with EMA. Further, the Notified Body has discretion as to whether to include the CDx manufacturer and medicinal product MAH/applicant in the pre-submission meeting. This is problematic, as the CDx manufacturer is best poised to answer any technical questions the EMA may have about the operation of the device and the analytical/clinical validation data present in the technical file. Additionally, the medicinal product MAH/applicant is best poised to answer any questions the EMA may have about the clinical study that will provide the clinical validation in a co-development scenario. As such, the Notified Body should be required to notify the CDx manufacturer as to the pre-submission activities and include the manufacturer in any pre-submission meetings. Proposed change:	The objective of a pre-submission meeting would be to agree on procedural and regulatory aspects of the CDx consultation, not to provide scientific input related to technical documentation to be submitted to the notified body or to the EMA. Clarification was added to the Guidance document. It would be up to the applicant of the CDx consultation, i.e. the notified body, to decide whether it would be relevant to include the CDx manufacturer and medicinal product MAH/applicant in the pre-submission meeting.

		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. Notified Bodies should consult with the CDx manufacturer when developing such questions. If additional guidance is needed, the notified body can request a pre-submission meeting with the rapporteur, ~~and, as appropriate,~~ which should also include the CDx manufacturer and the marketing authorisation holder(s)/applicant(s) of the medicinal product(s) (as applicable and relevant).	
162 - 163	3	Comment: One of the practical challenges for developers are unclear and/or opaque NB timelines, made particularly challenging in the current situation where NB resources are very stretched. The term 'early interaction' is very hard to interpret and inclusion of a set of months ahead of submission would be helpful to developers. Proposed change: The Agency recommends early interactions, **at least X months ahead of submission**, 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).	Partly accepted. Information was added to the Guidance to clarify that questions can be sent to the Agency **after receipt of the intention to submit letter** and will be addressed in writing to assist the notified body in preparing their application.
162	4	**Comment:** The document describes pre-submission activities in section 4.1. These activities focus on the administrative steps. They are only initiated by the Notified Body once it has received the submission by the device manufacturer. It is unclear whether the "early interactions" mentioned in line 162 are meant to include scientific advice early in the development process - or whether this part is confined to the period of time following the "intention to submit" letter.	The objective of the pre-submission interactions would be to agree on procedural and regulatory aspects of the CDx consultation, not to provide scientific input related to the technical documentation to be submitted to the notified body or to the EMA. Clarification was added to the Guidance document.

		Also, it is unclear from line 162 if the interactions can include early scientific advice questions with the device manufacturer (independently of the Notified Body). This is a question of great interest for device manufacturers as many would find this possibility helpful. Given that this guidance is dedicated to the interaction between the Notified Body and EMA, it could be appropriate for that question to be detailed elsewhere. **Proposed change:** The possibility to ask questions should be provided any time in the development process. Further clarity in the text concerning the scope of the interactions could be helpful as this section is raising many questions with our members. **Clarification request:** does "early interactions" suggest "initial consultation?" Early interactions (not defined but seems to be encouraged throughout the guidance) seem to suggest differently given there are multiple parties mentioned and encouraged whereby this guidance is strictly for "consultation" between EMA/NCA and NB? Proposed change: "Notified bodies are encouraged to have with the device manufacturer, the marketing authorisation holder(s) or applicant(s) of the medicinal product(s), (as applicable and relevant."	
162 - 168	5	Comment (technical): We welcome that EMA is open to early interaction between NB, CDx manufacturer and medicinal product applicant/MAH but the process needs to be further clarified: - What will be the pathway for the interaction? - As data owner and in scope of an expected application, the CDx manufacturer should also be able to directly address approval related questions to EMA to prepare relevant documentation (SSP and IFU)	The objective of the early interactions would be to agree on procedural and regulatory aspects of the CDx consultation, not to provide scientific input related to the technical documentation to be submitted to the notified body or to the EMA. Clarification was added to the Guidance document. See also responses to previous questions.

		- Clarify if the medicinal product applicant and CDx manufacturer can request an early interaction, i.e. without NB involvement. Proposed change (if any): More details of the process for the early interactions between EMA, NB, CDx manufacturer and medicinal product applicant should be added.	
162 - 168	5	Comment (general): The pre-submission consultation (and associated activities) is proposed to be possible only at the initiative of the notified body. It would be considered helpful if sponsors could also have the ability to trigger such pre-submission interaction. As such, the NB should be required to notify the CDx manufacturer as to the pre-submission activities and include the manufacturer in any pre-submission meetings. We also strongly recommend that EMA includes in the entire process the opportunity to involve both the manufacturer of the medicinal product and the CDx manufacturer as needed. Proposed change (if any): - The procedure for a pre-submission meeting in case a CDx manufacturer, MAH or applicant of the medicinal product need guidance on submission-related topics or CDx regulatory strategy should be included. - Proposal to reword: The Agency recommends early interactions with the relevant notified body, the device manufacturer, and the MAH(s) or applicant(s) of the medicinal product(s) (as applicable and relevant). Questions **arising during these interactions** 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. **Notified Bodies should consult with the CDx manufacturer when developing such**	Partly accepted. The objective of the pre-submission meetings would be to agree on procedural and regulatory aspects of the CDx consultation. Clarification was added to the Guidance document. It would be up to the applicant of the CDx consultation, i.e., the notified body, to decide whether it would be relevant to include the CDx manufacturer and medicinal product MAH/applicant in the pre-submission interactions. See also responses to previous questions.

		questions or at the very least notify the CDx manufacturer of the questions submitted. If additional guidance is needed, the notified body can request a pre-submission meeting with the rapporteur, ~~and, as appropriate~~, **which should also include** the **CDx manufacturer and the** marketing authorisation holder(s)/applicant(s) of the medicinal product(s) (as applicable and relevant).	
162 - 168	8	Comment: What are the anticipated timelines for the pre-submission meeting process between the Sponsor and Notified Body (e.g., can the pre-submission process begin prior to the "intent to submit letter", how long will it take to receive written feedback and scheduling a meeting, etc.) What types of questions can be presented to the Agency? Proposed change (if any): A pre-submission provides the opportunity for a submitter to obtain NB feedback prior to an intended technical file submission. The request should include specific questions regarding review issues related to a planned technical file submission. A pre-submission is appropriate when NB's feedback on specific questions is necessary to guide. The Sponsor can request a pre-submission meeting with the NB at prior to product development to align on the appropriateness of their analytical validation plan. The Sponsor may also request a pre-submission before the anticipated submission of their technical files to discuss any potential areas of conern prior to submitting or align on submission contents. It takes approximately 60-90 days for the NB to review the submission and provide a a written response to the Sponsor or schedule a teleconference to provide feedback. The purpose of the request is to define a pre-submission process with anticipated timelines, types of questions that can be submitted, who can initiate the meeting (device manufacturer, marketing authorisation	Not accepted. This Guidance document specifically focuses on the procedural aspects of the consultation to the European Medicines Agency by a notified body on a CDx and does not cover the complete conformity assessment performed by the notified body. The objective of the pre-submission interactions would be to agree on procedural and regulatory aspects of the CDx consultation (e.g., anticipated timelines), not to provide scientific input related to the technical documentation to be submitted to the notified body as this is out of scope of this consultation procedure based on the draft IFU and SSP. The Guidance document was revised to clarify the scope and timing of the pre-submission interactions. Furthermore, notified bodies are legally not in a position to provide scientific or technical advice to CDx manufacturers

		holder, NB), and how the feedback will be documented (e.g., written feedback, teleconference meeting minutes). Defining a pre-submission process will facilitate early communication and alignment to ensure devices are CE marked and available to patients in a timely manner.	related to product development and/or submission preparation.
165 - 168	5	Comment (technical): Include more details of the pre-submission meeting e.g. how soon before submission can this be conducted, can it be for advice for technical and scientific questions as well as regulatory questions, will there be timelines within which questions must be sent (and responses received), can one medicine have multiple consultations for pre-submission (i.e. when there are multiple NBs involved)? Proposed change (if any): Please include information on timelines, e.g. **All questions must be received within 2 months of planned submission. Responses will be provided by the Agency within 10 working days of receipt, unless otherwise communicated.'**	Accepted but slightly rephrased. The objective of the pre-submission interactions would be to agree on procedural and regulatory aspects of the CDx consultation, not to discuss the documentation to be submitted to the EMA. Clarification was added to the Guidance document.
166 - 168	4	**Comment:** "…, 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)." Since the client of the Notified Body (NB) is the IVD manufacturer, it does not make sense for the NB to request meeting without including the IVD manufacturer, as appropriate. The NB does not have agreement with marketing authorisation holder (MAH) unless the MAH is also the IVD manufacturer. **Proposed change:** Include IVD manufacturer.	The objective of the pre-submission interactions would be to agree on procedural and regulatory aspects of the CDx consultation, not to provide scientific input related to the technical documentation to be submitted to the notified body or to the EMA. Clarification was added to the Guidance document. It would be up to the applicant of the CDx consultation, i.e., the notified body, to decide whether it would be relevant to include the IVD manufacturer and medicinal

		Please provide reference to the mechanism for how the NB would request a pre-submission meeting with rapporteur? Or is this suggested by the provision of the EMA link below? Examples in the guidance for what could be discussed between NB and rapporteur could be helpful.	product MAH/applicant in the pre-submission meeting.
172	5	Comment (general): It is helpful to clarify in this section the contents of the dossier submitted by the NB (including draft Table of Contents) or to add a reference to where the information can be found. Proposed change (if any): Please add after line 211: **The application consists of a Cover letter, application form, draft IFU and draft SSP.** For follow-on devices, that are developed…..'	Accepted.
179 - 182	4	**Comment:** Consideration to assess the suitability of a CDx for use shall include analytical and clinical performance… Will this assessment only occur after the clinical trial completion? What information would be necessary in the pre-submission meeting?	The CDx consultation to medicines authorities is part of the conformity assessment by the Notified Body. It would be for the notified body to define at which timepoint of their review the consultation can take place. See previous comments on the scope of the pre-submission meeting. The objective of the pre-submission interactions would be to agree on procedural and regulatory aspects of the CDx consultation.
180 - 182	5	Comment (general): NBs are required to seek a scientific opinion on the suitability of the CDx with the concerned medicinal product(s), from the relevant competent authorities. This implementing guideline defines a fairly wide scope of review by the regulatory authority that includes "scientific rationale for biomarker selection, the analytical and clinical performance, the clinical	As specified in the Guidance, 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

		safety, and the clinical benefit to the patients (i.e. in terms of patient management and/or clinical outcome)". This appears to be a very broad review of the CDx documentation that could duplicate review performed by NBs, e.g. analytical/clinical performance is mentioned also in the scope of review by NBs as part of conformity assessment. The short time allotted to the consultation process (60 days) requires a specific focus on key aspects of interface between medicinal product and CDx. Proposed change (if any): It should be further clarified what specific aspects of the regulatory review of CDx should be the focus of the consultation process and what aspects remain the sole responsibility of the NB.	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). Further clarification was added to the Guidance based on the definitions provided in Article 2 of the IVDR.
180	7	Comment: With respect to 'analytical and clinical performance' also have to be considered in the assessment, but are in principle assessed by the NB. Nevertheless, for proper assessment, these data including the critical elements of study design and analysis have to be made available to EMA. It would be helpful for the Applicant as well as for the Assessor (and the NB) if it is made clear what is meant with analytical and clinical performance, exactly.	Accepted. Clarification was added to the Guidance based on the definitions provided in Article 2 of the IVDR. The updated Guidance also specifies that it is expected that the SSP follows the MDCG guidance 2022-9 - Summary of safety and performance Template.
181	1	*"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, 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)."* Proposed change (if any): Please include example(s) or an explanation of what is meant by "clinical safety" in the context of CDx assessment.	Reference to "clinical safety" was removed from the procedural guidance to ensure consistent terminology, in line with the IVDR.

181	4	**Comment:** the term 'clinical safety' is not an IVD Regulation concept. Please do not include new terms especially when they are not defined. We suspect that what is considered as 'clinical safety' should already be covered by 'clinical performance', a term which both is well understood for IVDs and is already listed here. **Proposed change:** Delete 'clinical safety'	Accepted. Reference to "clinical safety" was removed from the procedural guidance to ensure consistent terminology, in line with the IVDR.
181	5	Comment (general): Please provide example(s) or an explanation of what is meant by "clinical safety" in the context of CDx assessment. Proposed change (if any):	Reference to "clinical safety" was removed from the procedural guidance to ensure consistent terminology, in line with the IVDR.
181	7	Comment: From this brief description 'the clinical safety' it is unclear what safety is meant. To our opinion this should relate to safety of the accompanying medicinal product when used together with the CDx, and not of the CDx itself. Proposed change (if any): It is advised to clarify this statement.	Reference to "clinical safety" was removed from the procedural guidance to ensure consistent terminology, in line with the IVDR.
187 - 203	4	**Comment:** the guidance is indicating only co-development or follow-on development as existing pathways for the development of Companion Diagnostics (CDx) (aside from the transition of existing IVD tests marketed under the IVDD.) However, there are many other situations leading to the development of a CDx. The current guidance should be expanded to take into consideration these situations. **Proposed change:** The following scenarios are examples envisaged in the context of the CHMP/CAT consultation procedure on the CDx. The guidance should be updated to note that the various scenarios are given	Accepted. The descriptions of possible scenarios for CDx development were revised and it was clarified that there could be other situations not covered by the current guidance.

		as examples. EMA should consider reviewing their processes and fees in light of the various scenarios: • Co-developed CDx: A device that is co-developed with a medicinal product, whereby both are designed to be part of the same trial. Trial outcome leads to evidence for each product. The drug and device need approval and certification to be placed on the market at the same time. They might be expected to be reviewed by the same EMA committee at or around the same time. • Follow-on 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. • Next generation CDx, whereby a new generation of diagnostic test replaces an older one (e.g. due to a new testing platform). • For an existing CDx: there is an extension of the intended use for a new drug indication or by inclusion of new markers as part of the analysis. • The medicinal product(s) are already approved and on the market. The CDx is developed to determine which patients could	

		have the best outcomes and/or avoid side effects. The MAH may or may not be aware of this initiative and claim by the IVD manufacturer. 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 scenarios above are possible depending on how the device was initially developed.	
189	4	**Comment:** The co-developed device is not really described at all, only mentioned. A co-developed CDx will be/have been included as such during medicinal product application review. In a co-review situation, it is impractical to adhere to the pre-approval activities without creating a gap to market availability of medicinal product and CDx. **Proposed change:** Suggest that for co-developed devices where the medicinal product is undergoing review by the same EMA committee(s) and rapporteur, discussions between EMA and MAH may be referenced in pre-submission activities (intention to submit letter) and allow for less than 3 months' notice to be provided.	Partly accepted. The guidance was updated to clarify the description of co-developed devices. More information about the timing of the medicinal product marketing authorisation application and the CDx consultation was included in Section 4.1.
189	5	Comment (general): Similar to the Follow-on device, a definition of the Co-developed device would be helpful. Alternatively, a definition section could be added at the end. We would like to point out that even though co-developed, the total number of subjects in the medicinal product clinical study report may be larger than the total number of subjects in the diagnostic clinical study report (as there is a 'bridge' between the clinical trial assay and the CDx). This difference could be explained within the diagnostic clinical study report.	Accepted but slightly rephrased. The guidance was updated to clarify the description of co-developed devices.

		Proposed change (if any): A device that is co-developed with a medicinal product**, which can either be developed by using a companion diagnostic prototype to select patients for enrollment into the clinical trial of the corresponding medicinal product or by conducting a bridging study assessing the concordance of the CDx and the clinical trial assay used in the clinical trial of the corresponding medicinal product.**	
190 – 195; 201 - 203	4	**Comment:** It would be helpful to clarify if the original CDx for a follow-on CDx needs to be authorised under the IVDR process, or if a manufacturer can use demonstration of concordance with a device already marketed under Directive 98/79/EC, that would be considered a CDx under IVDR (in light of the definition under Article 2) but does not yet have CE-marking under IVDR. **Proposed change:** Clarify situation for follow-on CDx with regard to status of original CDx	Please see the recently published MDCG guidance: https://ec.europa.eu/health/document/download/59abcc81-fd32-4546-a340-24c8fad4e2ac_en?filename=mdcg_2022-10_en.pdf entitled: *"Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)"*
191	7	Comment: Suggest to modify this sentence as follows: …CDx is a device that seeks the same ~~therapeutic~~ **diagnostic** indication **for** ~~in~~ its intended use	Partly accepted. 'Therapeutic' was removed.
194	7	Comment: It is unclear what safety refers to in the context of CDx. Proposed change (if any): If this relates to the safety of the CDx itself (and not of the medicinal product when used together with the CDx), it should be clarified which safety issues related to the CDx are to be considered. The following change may be considered: '*The **diagnostic performance, and therefore the consequential** safety and*	Accepted.

		*effectiveness of **the associated medicinal product**, of a follow-on CDx should therefore be highly comparable to the original CDx'*	
196	1	*"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."* Comment: The current procedural guidance is focussed on interaction between the various stakeholders for a CDx. However, it also briefly refers to scientific concepts for which additional guidance is urgently needed. Although we recognise that this is outside the scope of this procedural guidance we strongly request EMA to provide further clarification (**e.g in a dedicated Q&A**) on the following aspects mentioned in this guidance: - Which kind of "concordance/equivalence studies" would be required to show interchangeability between assays? Please elaborate on alternative scenarios (addressed with "***might** need to be conducted*"). - Under *"The aspects that are considered when assessing the suitability of a CDx for use with the concerned medicinal product(s)"* please detail which ones of these and how they are to be assessed for "*concordance/equivalence studies*": a) clinical performance, b) clinical safety, c) clinical benefit to the patients.	This comment is noted. Based on experience gained from the initial consultations, the need for further guidance might be considered.
196 - 199	2	Comment: We support the notion that concordance studies may be sufficient for follow-on CDx, particularly in cases where clinical samples from the co-	This comment is noted.

		development study may not be available. This will increase the number of available CDx and the ability for patients to be tested for the relevant biomarker. Proposed change: No change.	
196 - 200	5	Comment (technical): The mention of a need for clinical trial or re-test of samples or, in absence of those, the needs for concordance/equivalent studies seems to go beyond the requirements established in IVDR since the appropriateness of the claimed equivalence must be assessed by NB during the TD assessment: Proposed change (if any): Please delete lines 196-200 or add clarification that the NB's conclusion of the equivalence should be considered in the consultation.	Accepted.
196 - 200	7	A clinical trial may not be necessary, a comparison of the diagnostic performance may eb sufficient. It is proposed to amend the text as indicated below: '*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.*'	Accepted. The description of follow-on devices was revised in the Guidance.
206	7	It is unclear if 'application dossier' concerns the application dossier for the consultation or for the concerned medicinal product.	This sentence referred to the application dossier for the CDx consultation, but the text was removed to avoid repetition in the Guidance.

207 - 208	4	**Comment:** the terms 'device measurement characteristics' and 'device development characteristics' are not IVD Regulation concepts. Please do not include new terms, especially when they are not defined. We suspect that 'device measurement characteristics' is covered by the term 'analytical performance', which is already listed here. **Proposed change:** Delete 'device measurement characteristics' and 'device development characteristics'	Accepted. This sentence was removed from the Guidance document.
208 - 211	1	*"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)."* Comment: - Clarification is required: Does the statement mean that the summary of the results/data for the medicinal product in the SSP and IFU will be considered sufficient because in-depth assessment is provided in the eCTD? Because in-depth assessment of the data for the device should not be performed by EMA as part of the assessment of the medicinal product. This would create unnecessary duplication. Proposed change (if any): 'the summary of the results/data for the medicinal product in the SSP and IFU will be considered sufficient because in-depth assessment is largely performed as part of '	Reference to the assessment of the marketing authorisation application(s) for the concerned medicinal product(s) was removed to clarify that the CDx consultation is a stand-alone procedure based on information provided in the SSP and IFU.
208 - 211	2	Comment: We support the notion that only a summary of the clinical study and a reference to the medicinal product application (in a co-development	The comment is noted but this sentence was removed because the CDx consultation is a stand-alone procedure initiated by the notified body to the EMA based on

		scenario) needs to be included in the application dossier for the CDx. This is an improvement over CDx submissions in other regions, and will prevent delays in submitting the application dossier for the CDx, which will ultimately make it more likely the CDx will be ready and potentially available at the time of drug approval. In our experience, when the CDx manufacturer has to wait for the clinical study report from the medicinal product MAH/applicant and then transcribe it into a clinical study report for the device application, this causes unnecessary delay in the submission of the CDx application. Proposed change: No change.	information provided in the draft SSP and IFU.
208 - 211	5	Comment (general): Clarification is required: It is assumed that 'the summary of the results/data in the SSP and IFU will be considered sufficient because in-depth assessment is largely performed as part of '… refers to the medicinal product? Because in-depth assessment of the data for the CDx should not be performed by EMA as part of the assessment of the medicinal product. This would create unnecessary duplication. Please clarify. Proposed change (if any): ' the summary of the results/data **of the medicinal product** in the SSP and IFU will be considered sufficient because in-depth assessment is provided in the eCTD.	Reference to the assessment of the marketing authorisation application(s) for the concerned medicinal product(s) was removed to clarify that the CDx consultation is a stand-alone procedure based on information provided in the SSP and IFU.
208	7	Comment: With reference to 'analytical and clinical performance'. It is not very clear what is exactly meant. A reference to a PfC or GL on performing test research/diagnostic studies may be helpful.	Accepted. Clarification was added to the Guidance based on the definitions provided in Article 2 of the IVDR.

210 - 211	6	Comment: Please consider expanding on the level of information to be provided for in-depth assessment of the CDx by the EMA during assessment of the concerned medicinal product, or cross-reference to existing guidance. For instance, reference to the EMA *Day 80 assessment report – Clinical template with guidance* (day-80-assessment-report-clinical-template-guidance-rev-05-21_en.docx (live.com)) would assist device manufacturers and medicinal product applicants in understanding the information that may be included in the medicinal product marketing authorisation application.	Reference to the assessment of the marketing authorisation application(s) for the concerned medicinal product(s) was removed to clarify that the CDx consultation is a stand-alone procedure based on information provided in the SSP and IFU.
214 - 219	3	Comment: To avoid the risk of confusion due to variable expectations of what to provide regarding analytical and clinical performance in the SSP and IFU, it would be helpful if the words *'sufficient level of information'* in this sentence are replaced with a more specific set of expectations. This would improve clarity by driving consistency in these public facing documents. Proposed change: 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.	This sentence was removed from the Guidance as the contents of the SSP and IFU is set out by the IVDR.
217 - 219	4	**Comment:** "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 purpose of the IFU and SSP is not EMA consultation but user and public information. The elements of each of these documents further is clearly spelled out under the IVD Regulation. IFU and SSP normally should be sufficient for the assessment of suitability. The assessment of	This sentence was removed from the Guidance as the contents of the SSP and IFU is set out by the IVDR.

		performance should be the remit of the Notified Body. Additional data should not be added up front to IFU and SSP as a matter of course. If additional information is required – this should be for the isolated case. Where EMA requires information other than what is mandated by the IVDR in the IFU and SSP, this information should be provided by a different route and not requested in the (to be) public documents. MedTech Europe is concerned that the current wording may cause notified bodies to request more information be placed into the IFU or SSP than intended by IVDR. In the future, it would be helpful for MDCG and EMA to develop guidance on SSP for companion diagnostics. **Proposed change**: Delete this phrase or make it clear in the assessment report template that if information is required in more detail for purposes of consultation than what is provided in draft IFU/SSP, such request should be for the isolated case and be provided independently of the draft IFU/SSP.	
217 - 221	5	Comment (editorial): To avoid the risk of confusion due to variable expectations of what to provide regarding analytical and clinical performance in the SSP and IFU, it would be helpful if the words 'sufficient level of information' in this sentence are replaced with a more specific set of expectations. This would improve clarity by driving consistency in these public facing documents. Proposed change (if any): Please provide more precise information on the level of information expected.	This sentence was removed from the Guidance as the contents of the SSP and IFU is set out by the IVDR. The updated Guidance also specifies that it is expected that the SSP follows the MDCG guidance 2022-9 - Summary of safety and performance Template.

222	1	*Regarding 4.3 Consultation procedure to the European Medicines Agency* Comment: - It is of utmost importance for European patients with unmet medical needs to have access to innovative treatments as early as possible. However, if adequate testing is not available by the time the product is approved, the access will be hampered. Especially for accelerated assessment procedures potential detrimental consequences have to be avoided if there is no simultaneous assessment of CDx and medicinal product. Scenarios for accelerating CDx review should be considered. - Please clarify what happens if the second 60-day extension term passes by without the approval ("opinion") being finalized/issued. Has the NB to apply again? Is there any further possibility of an extension? - Please elaborate on how divergent opinions of EMA & NB will be resolved. Please explain what is meant by "due consideration"; does it imply an obligation for NB to motivate a decision which would not reflect EMA's opinion? Proposed change (if any): Please include a flowchart of the different assessment steps/timetable for the procedure.	Additional information was added to clarify that the timetables for the submission of 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. An opinion (positive or negative) for the consultation procedure for the CDx will be issued at the latest by the end of the extension period. The notified body should take into consideration the scientific opinion on the suitability of the device in relation to the medicinal product concerned prior to granting the device certification.
222	5	Comment (general): Apart from the presubmission meeting and the payment of fees, involvement of the CDx manufacturer and the applicant/MAH of the medicinal product in the consultation is not specified. It would be important for the CDx manufacturer and the applicant/MAH to be informed throughout the procedure, particularly in case a list of questions is generated after the first round of 60-day assessment, in	Partly accepted. The Guidance was revised to clarify that a list of questions may be issued to be addressed by the notified body, if further clarification is needed for the CHMP to conclude on the suitability of a CDx for use with the concerned medicinal product(s). It is in the remit of the NB to

		case there will be an extension of the assessment by another 60 days, or in case the outcome of the suitability assessment is negative. Proposed change (if any): Specify if and how the medicinal product applicant/MAH and the CDx manufacturer will be informed throughout the procedure, particularly in case: (1) a list of questions are generated after the first round of 60-day assessment, (2) there will be an extension of the assessment by another 60 days (and the related reasons), or (3) the outcome of the suitability assessment is negative. For example: In case of 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 the consultation procedure is extended, the Notified Body shall communicate this to the CDx manufacturer.**	interact with the device manufacturer, as needed. The MAHs and applicants of medicinal products will not be involved directly in the CDx consultation. It is the responsibility of the MAH/applicant and device manufacturer to coordinate sharing of information about their respective applications and keep each other informed on steps of their applications.
222 - 244	5	Comment (general): This section would benefit from a number of clarifications: - Please clarify what happens if the second 60-day extension term passes by without the approval ("opinion") being finalized/issued. Has the NB to apply again? Is there any further feasibility for extension? - It would be helpful to include a flowchart of the different assessment steps/timetable for the procedure. It would also be helpful to provide further detail on how the CDx consultation timeline would fit with the medicine centralised procedure standard review timetable as this would facilitate parallel assessment of the medicine and consultation of the CDx if needed. - Please clarify and/or provide examples for what could be considered "justified grounds" for extending timelines. It would be important to keep the initial 60 days as the normal timelines for opinion and an extension as exceptional.	Additional information was added to clarify that the timetables for the submission of 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. An opinion (positive or negative) for the consultation procedure for the CDx will be issued at the latest by the end of the extension period. The justified grounds will need to be determined on a case-by-case basis. The Guidance was revised to clarify that a list of questions may be issued to be addressed by the notified body and at his discretion with

		- Please consider including the option, in case of an extension, that the opinion is issued a.s.a.p during the extension, i.e. where there is no need to use the whole 60-day extension, CHMP/CAT should strive to issue the opinion earlier. This is particularly important in the framework of accelerated assessment procedures for medicinal product approvals. Proposed change (if any):	the involvement of the CDx manufacturer if further clarification is needed for the CHMP to conclude on the suitability of a CDx for use with the concerned medicinal product(s). Efforts will be made to issue the opinion as soon as possible during the extension.
223 - 224	2	Comment: Guidance needs to explicitly reflect the need for Notified Bodies to be appropriately designated to carry out conformity assessments according to IVD legislation Proposed change (if any): The applicant for the consultation procedure must be a notified body duly designated to carry out conformity assessment according to the provisions of Regulation (EU) 2017/746	Accepted. The Guidance was revised accordingly.
225 - 229	2	Comment: The document does not describe how the CDx manufacturer will be notified if the consultation procedure is extended by an additional 60 days. It should be clarified whether a clock-stop period is foreseen between the first and the second 60-days period. If not, it could be clarified how much time notified bodies have to address the medicinal products authority's questions (if this time is included as part of the second 60 days period). This is critical information that must be shared with the CDx manufacturer, who may have legal obligations (by contract) to inform	As per the wording of the legal provision, there will not be a clock-stop between the first and the second 60-day period. Clarification regarding the timelines for the CDx consultation was added to the Guidance and specific timetables for CDx consultations have been published on the EMA webpage. The proposal to add the additional sentence is not accepted as it would be the remit of the relevant Notified Body to decide on communicating any extension of the consultation to the CDx manufacturer.

		the medicinal product MAH/applicant of regulator review timelines and potential delays to the approval or launch of the CDx. Additionally, the consultation extension of 60 days will significantly delay the launch of a medicine, with a critical impact on patients especially on areas of unmet medical need. Therefore, it is critical that the CDx manufacturer is informed, so the medicinal product MAH/applicant can be duly informed as well. Suggest modifying to note that the Notified Body will communicate this extension to the CDx manufacturer once the decision to extend has been made. Proposed change: 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. <u>If the consultation procedure is extended, the Notified Body shall communicate this to the CDx manufacturer.</u>	
225 - 229	3	Comment: The timetable provides for a 60 day assessment with a 60 day extension. It is suggested to clarify if the additional 60 days includes time for NB to provide clarification or if this is in addition. If in addition, a timeframe for NB clarification to be provided to EMA would be useful.	Accepted. Clarification was added to the guidance.
225	4	**Comment**: The timeline for delivery of the opinion is 60 days for EMA - not for specific committees within EMA. In case there are further administrative steps needed (?) to issue the EMA Scientific Opinion, after the relevant committees have done their work, this should be accounted for within the 60 days timeline. **Proposed change**: Replace '*The CAT/CHMP assessment will follow a 60-day timetable'*	Accepted but slightly rephrased because the EMA will provide its opinion within 60 days of the start of the procedure.

		with '*The EMA will provide its opinion within 60 days of receipt of all the necessary documentation*'.	
225; 241-242	4	**Comment:** we see timetables for the 60-day consultation are provided on EMA's website, for example this one: Timetable: Companion Diagnostic Initial Consultation (europa.eu). Given that a considerable level of detail is provided in the timetables about process and timing to arrive at a scientific opinion, it would really help to clarify the process for all readers by providing a link to the timetables and or including an indicative example into the guidance. For example, the timetables provide a submission date and a start date. Lines 241-241 refer to 'CAT/CHMP timetable' without explaining that actual timetables exist and are publicly available. A lot of mysteries were solved when we found one of these. **Proposed change**: include a link to the timetables in the guidance and or describe the various steps with indicative timelines or an example of a 60-day timeline. For a future version of this document, a flowchart or visual process would be helpful however inclusion of one for this version should not slow down publication of this guidance.	Accepted. Further information and a link to the timetables was included in the Guidance.
225 - 229	4	**Comment**: The goal of the process should be to determine suitability within the 60-day timeframe. Extension for an additional 60 days should ideally be limited to cases where there are questions about the suitability and more information or discussion is needed. Justification for the extension should be provided to the notified body before the extension starts, e.g., request for supplemental information or notification that more time is needed to address open questions. Notification that a further 60 days is needed, will help the Notified Body	Accepted. Information was added to the guidance to explain that 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 his discretion with the involvement of the CDx

		and the device manufacturer to plan ahead, including where needed to reschedule labelling, production and device supply. **Proposed change**: Justification for the extension should be provided to the notified body before the extension starts, e.g., request for supplemental information or notification that more time is needed to address open questions.	manufacturer , within a given timeframe as part of the extension period.
225 - 232	5	Comment (technical): For reviews that will involve an ATMP, CHMP will base its opinion on the previous draft CAT opinion. Would the overall review time still be max 60 days, or could there be potential extra days? Proposed change (if any): Please clarify.	The overall review time will still be maximum 60 days with a possible extension of 60 days. A link to the timetables was included in the Guidance.
226	4	**Comment:** The list of references is not complete. Particularly because the IVD sector is so new and unfamiliar with EMA's various and already existing procedures and guidance documents – it would be great to have a complete list of references for all relevant sources which are mentioned in the text. **Proposed change:** Include references for 60-day consultation timelines (CHMP and CAT), fees (Regulation (EC) 297/95; explanatory note, SME guide, EMA website reference…), application form, EMA website sections which are relevant for CDx	The comment has been taken into account.
230	1	*"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."* Proposed change (if any): Please include information on Transparency. We assume that minimum information on the CDx assessment will be included in the EPAR?	- The CDx suitability opinion is an independent separate procedure from the medicinal product, thus the EPAR will not include information from the CDx consultation. However, please note that for medicinal products requiring the use of a biomarker, this will be reflected in the EPAR.

230	5	Comment (general): *"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."* - Please include information on Transparency. We assume that minimum information on the CDx assessment will be included in the EPAR. - Please include the mechanism for relaying this opinion back to the licence owner of the medicinal product - If the CDx will be used in a clinical trial, will the Agency archive the opinion in the CTIS as well? Proposed change (if any):	- The CDx suitability opinion is an independent separate procedure from the medicinal product, thus the EPAR will not include information from the CDx consultation. However, please note that for medicinal products requiring the use of a biomarker, this will be reflected in the EPAR. - It is the responsibility of the MAH/applicant and device manufacturer to share information about their respective applications and keep each other informed on steps of their applications. - This consultation takes place in the context of the certification of the device by the notified body and is not linked with the approval of the clinical trial in which the device might be used, and therefore is not included in the CTIS.
230 - 233	5	Comment (general): No mention is made about a potential clarification meeting e.g if the EMA (or other consulting agency) has any technical questions relating to the medicinal product. A similar stakeholder involvement as for presubmission meeting is suggested. Proposed change (if any): Specify if a clarification meeting with medicinal product applicant/MAH and the CDx manufacturer is possible throughout the procedure.	Not accepted. A clarification meeting with medicinal product applicant/MAH and the CDx manufacturer is not foreseen for CDx consultations. However, if the EMA has any questions relating to the medicinal product, these should be addressed as part of the marketing authorisation application.
231	7	Comment: Please clarify if the advice will be discussed at CHMP prior to sending it out	The rapporteur assessment report will be discussed at the CHMP plenary meeting, in

			case there are issues that need further consideration and to reach a CHMP position.
233 - 234/101	5	Comment (technical): "*The notified body will give due consideration....* " Proposed change (if any): - Specify to which extent the NB will consider the opinion provided by the medicinal products authority/EMA and what process is followed in case of discrepant opinions. - Specify the timeline by when the NB will inform the EMA about its decision as well as the format and content of the communication.	The notified body should take into consideration the scientific opinion on the suitability of the device in relation to the medicinal product concerned prior to granting the device certification. The notified body should send a formal notification to the product lead and rapporteur for the CDx once they made their final decision on the certification of the device. The Guidance has been revised accordingly.
235 - 237	1	*"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."* Comment: While we understand that there is no legal requirement for simultaneous approval of the medicinal product and CDx, EMA and NB should nonetheless make every effort to provide the device certification earlier than, or at least simultaneously with, the Medicinal Product approval where the application procedures are running in parallel. It is of utmost importance for European patients with unmet medical needs to have access to innovative treatments as early as possible. However, if adequate testing is not available in time when the product is approved, the access will be hampered.	The EMA and notified bodies will aim to avoid any delays in device certification or medicinal product approval where the application procedures are running in parallel. However, it will the responsibility of the CDx manufacturer and medicinal product MAH/applicant to interact early with both the notified body and the EMA to ensure timely access to treatments for European patients with unmet medical needs.
235 - 237	2	Comment:	As mentioned in the Guidance, there is no legal requirement that the medicinal

		Time points for the start of CDx consultation procedures should better reflect the difference between a co-developed CDx, 'Follow-on' devices, and devices already marketed as IVDD's. If co-developed there should be a requirement to submit device certification at the time of MAA as by definition a companion diagnostic is a device which is essential for the safe and effective use of a corresponding medicinal product. Proposed change (if any): Clarify guidance in line with EMA/37991/2019 'Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)' (2.5.) *At what stage of the MAA do I need to submit the notified body opinion? Rev. June 2021* "EMA/NCAs strongly recommend submitting the EU certificate declaration of conformity/notified body opinion already in the dossier of the initial marketing authorisation application for the medicinal product to facilitate a smooth running of the procedure. In case the applicant cannot provide the required documentation at the time of MAA submission, the relevant documents must be provided before an opinion on the medicinal product application can be issued. Applicants should discuss their plans to provide the required documentation during the EMA/NCA pre-submission meeting. The absence of the required documentation may result in additional clock stops during the procedure".	product approval and the device certification are simultaneous.
235 - 242	4	**Comment:** This section states that devices that are already on the market or are follow-on devices are independent of the medicinal products procedure and may start the CDx consultation at any time. This might also be the case for co-developed devices. We note that the device submission	The guidance document was revised to clarify the timetables for assessment and avoid any misunderstanding regarding the different scenarios.

		should be sufficient for EMA to make their opinion. The data necessary to make assessment if patients are correctly selected, should be in the draft SSP, which would usually be based on as late trial data as possible. The moment at which the device manufacturer has strong trial data might come at an earlier stage (e.g. CDx which identifies patient population to prevent an obvious and significantly adverse side effect from the therapy may have that data relatively early on in the clinical trials process).	
235 - 237	5	Comment (general): It is stated that the there is "no legal requirement for simultaneous approval of medicinal product and device certification". Even if this is not legally required, there is an urge to ensure coordination of those processes to ensure as much as possible that medicinal product approvals lead effectively to patients being able to receive such treatment and addressing clinical and public health needs. Therefore it would be valuable for all stakeholders to set an approximate timetable that can ensure as much as possible that all necessary steps are completed in a timely manner with the aim to achieve a simultaneous approval of medicinal product and CDx. This is of particular importance in the framework of products reviewed under accelerated assessment which mostly address urgent unmet needs and for which expediting medicinal review would have limited advantage if the corresponding CDx cannot be made available in a timely manner. Proposed change (if any): Please ensure a process is in place at the EU-level (Centralised Procedure, EMA) and NBs to coordinate the medicinal product and CDx' approval pathways in order to ensure the availability of the medicinal product and the CDx around the same time.	The EMA and notified bodies will aim to avoid any delays in device certification or medicinal product approval where the application procedures are running in parallel. However, it will be the responsibility of the CDx manufacturer and medicinal product MAH/applicant to interact early with both the notified body and the EMA to ensure timely access to treatments for European patients with unmet medical needs. The guidance was revised to also address medicinal products reviewed under accelerated assessment.
235 - 239	5	Comment (technical):	The EMA and notified bodies will aim to avoid any delays in device certification or

		The guidance does not address the situation where the medicinal product is in an accelerated procedure and how will approval of the companion diagnostic be handled? Will accelerated review of the CDx be initiated? Proposed change (if any): The co-review pathways will be closely co-ordinated by EMA/NCAs and NBs with possible acceleration for the CDx were warranted so that there is no delay for medicinal products that make use of an accelerated pathway.	medicinal product approval where the application procedures are running in parallel. However, it will be the responsibility of the CDx manufacturer and medicinal product MAH/applicant to interact early with both the notified body and the EMA to ensure timely access to treatments for European patients with unmet medical needs. The guidance was revised to also address medicinal products reviewed under accelerated assessment.
235 - 239	8	Comment: For co-developed devices, does issuance of the EU technical documentation assessment certificate by a NB occur in parallel to the approval of the corresponding medicinal product, if both the application for the assessment of the technical documentation and the application for the authorization of the medicinal product are undergoing a parallel review? For co-developed devices, does the EMA have to be at a certain stage of the medicinal product review in order to be able to give an opinion to the NB on the suitability of the device in relation to the medicinal product? Proposed change (if any): For co-developed devices, the EMA should have completed at least the primary review of the medicinal product the medicinal product submission in order to be able to give an opinion to the NB on the suitability of the device in relation to the medicinal product. Although EMA's opinion to the NB on the suitability of the device may come at any time during the conformity assessment process, the final medicinal product approval and device certification will come at the same time.	Not accepted as there is no such defined timeframe in the IVDR. In order to optimize this consultation process, the Agency highly recommends early interactions between the Agency, the relevant notified body, the device manufacturer and the MAH/applicant for the medicinal product to agree on the timing for the CDx consultation procedure.

		Having anticipated timelines for device manufacturers allows for better planning and coordination with the NB to ensure devices are CE marked and available to patients in a timely manner. Additionally, as previously noted, neither the drug nor the CDx can be used on it's own to treat patients. As such, concurrant approval of the medicinal product and device certification is a reasonable approach.	
236 - 237	4	**Comment:** 'there is no legal requirement that the medicinal product approval and the device certification are simultaneous.' Also see above comment. **Proposed change**: Can it be clarified that the European Medicines Agency may give an opinion on suitability of the CDx before the review of the medicinal product marketing authorisation is complete?	This would need to be assessed on a case-by-case basis.
237 - 239	5	Comment (general): Interactions should involve also the applicant/MAH of the medicinal product and the CDx manufacturer so they are aware. Proposed change (if any): Change to state early interactions to agree a submission date for the CDx consultation procedure should also include the medicinal product applicant/MAH and the CDx manufacturer.	Not accepted. It would be up to the applicant of the CDx consultation, i.e. the notified body, to decide whether it would be relevant to include the CDx manufacturer and medicinal product MAH/applicant in the pre-submission interactions.
237 - 239	7	Comment: When the consultation procedure for a co-developed CDx would start at the same the time as the MAA for the concerning medicinal product, CHMP may not be in a position to provided adequate scientific advice with the 60 day time period, since this is dependent on information assessed during the MAA.	Not accepted as there is no such defined timeframe in the IVDR. In order to optimize this consultation process, the Agency highly recommends early interactions between the Agency and

		Proposed change (if any): Therefore, for co-developed CDx, it is proposed to add the following statement: '*Since the MAA data package is of relevance for the CHMP to be in the position to provide an opinion on the suitability of the device with the medicinal product, it is advised that the CDx consultation procedure will start only after at least the first round of the medicinal product initial MAA evaluation or extension of indication, as applicable*.'	the relevant notified body to agree on the submission date for the CDx consultation.
246 - 248	4	**Comment:** Not every intended use change for a CDx shall require consultation of the EMA - only those that are in relation to the CDx intended purpose and performance or where there could be impact on the suitability of the device. What happens when the CDx device has a change which is extended to a non-CDx claim, e.g. intended for use to monitor disease progression? This should not involve the EMA through this procedure (unless that change were to impact the overall performance including the CDx part). **Proposed change:** Please add clarification for extension of non-CDx intended purpose	Not accepted. This is addressed in the first sentence of this paragraph and is considered sufficiently clear.
246	5	Comment (editorial): Please acknowledge that CDx may also be certified via the type examination (Annex X) procedure. Proposed change (if any): Line 246: In accordance with point (f) of Section 5.2 of Annex IX **and Section 5.5 of Annex X** of the IVDR Line 250: … in case it identifies the need for a supplement to the EU technical documentation assessment certificate **or to the EU type-examination certificate**.	Accepted.
246 - 248	5	Comment (general):	This step is not in the remit of the medicines regulators.

		Manufacturers should be able to propose (and justify with appropriate evidence) whether a change actually impacts the intended use or suitability of the device for use with the medicinal product. We also propose to provide guidance on criteria that will trigger EMA involvement to ensure a standardised approach by different NBs. Proposed change (if any): ……the manufacturer must inform the notified body of the changes **and provide the manufacturer's assessment, with appropriate justification and evidence, as to whether the change requires a new conformity assessment or supplement to the technical documentation.** The notified body must assess…..'.	
246 - 251	7	Comment: It is noted that only a short 30 day timetable is indicated for variations. This may pose problems in case of major variations.	This comment is noted. However, the timeline for issuing the EMA/CHMP opinion on a 'follow-up consultation' is 30 days according the IVDR. To enable planning for assessment teams, information was added to the Guidance to explain that 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 Agency. This can be achieved by means of an email to the product lead and the rapporteur, specifying the scope and the submission date of the intended application. The information will be used for planning purposes by the Agency and the Rapporteurs' assessment teams.

248 - 250	6	Comment: Please consider amending to provide specific information on the principles that apply. For instance, would an "intention to submit letter" be required for post-consultation phase reviews by the EMA? If yes, would the same timeframe (at least 3 months before planned submission date) apply or could this timeframe be reduced, due to the reduction in scope for a post-consultation phase review?	Clarification was added to the guidance. See also previous comment.
250 - 251	4	**Comment:** Please clarify that the 3-month notice will not apply to the post-consultation phase. It will be impracticable for manufacturers to factor this additional notice period into changes. Also, the time given for EMA provide its opinion is shorter than for the initial consultation: within 30 days of receipt of the necessary documentation regarding the changes. **Proposed change:** Please clarify the timeline, if any, for the Notified Body to provide advance notice to the EMA during the post-consultation phase.	Clarification was added to the guidance. See also previous comment.
257	5	Comment (general): The rules relating to the fees payable to the European Medicines Agency for consultations on medical devices are established in Council Regulation (EC) No 297/95 Would the fee for this consultation be the full fee under (EC) No 297/95 i.e. 70,000 Eur? What would the medicinal product's licence owners liability be for these fees? Proposed change (if any):	The fees for medical device consultations are laid down in Section 2 of Annex II to the Implementing Rules to the Fee Regulation. As stated in said Rules, the total amount of the fees to be paid for a specific consultation may depend on certain factors, such as the number of active substances involved and whether it is an initial request or a follow-up request. Furthermore, the fees for medical device consultations are charged to the medical device manufacturer, as clarified in Section 1.4 of the Explanatory note on general fees payable to the European Medicines Agency,

			which states: "*The fees payable for consultations on medical devices shall be charged to the medical device manufacturer that, according to the application form submitted to the Agency, requested the assessment of conformity of the medical device by the notified body on the basis of which the consultation is applied for*."
263 - 264	4	**Comment:** Presumably the fees for the consultation are charged to the Notified Body and not directly to the device manufacturer. The link provided with information on how to register with the EMA as an SME is specific for SMEs operating in the pharmaceutical sector. **Proposed change:** Can it be clarified if/how a medical device manufacturer can register as an SME and benefit from fee reductions? Also, consider updating the SME user guide to include medical devices and IVDs.	The fees for medical device consultations are charged to the medical device manufacturer, as clarified in Section 1.4 of the Explanatory note on general fees payable to the European Medicines Agency. The current reference to the SME user guide provides sufficient information on the process for requesting SME status.
EMA APPLICATION FORM Section 2.1.5	4	**Comment**: Questionable if there is enough basis in IVDR to request the NB (and indirectly the manufacturer) to provide 'details of the other medical device(s) used in the concordance study(ies)'. Rather, such information could be added where deemed appropriate by the IVD manufacturer. Does 'other medical device(s)' mean other IVDs? **Proposed change**: Potentially delete this part or make it clear that this is optional information which may be included: 'Details of the other medical device(s) used in the concordance study(ies) Name of the medical device:	This comment is noted. High-level information about any other medical device(s) used in the concordance study(ies) for follow-on device is expected to be provided in the application form.

		Short description of the medical device: ‘	
EMA ASSESSMENT REPORT TEMPLATE **Section 1.1**	4	**Comment**: The term ‘consultation’ is not further defined and could mislead the audience of the guidance as to what kind of consultation is requested. Therefore, we suggest using the term in the IVDR, ‘scientific opinion regarding the suitability of the device’ (in relation to the medicinal product concerned). **Proposed change**: Replace ‘*an application for consultation on the suitability of the device [...]’* with ‘*an application for a **scientific opinion regarding the** suitability of the device….[...*]’	Accepted.
EMA ASSESSMENT REPORT TEMPLATE Section 1.2 Table, Row 4-7	4	**Comment**: The goal of the 60-day consultation for a scientific opinion with EMA should be to evaluate suitability of the companion diagnostic with the medicinal product(s) concerned, based on the draft IFU and SSP. In light of the limited amounts of documents to be submitted (draft IFU and draft SSP), including internal steps into the standard template for requesting supplementary information seem disproportionate. At the very least, requests for supplemental information should be reserved for isolated cases rather than becoming a standard process. Should such a request nonetheless be deemed necessary and where it would result in a 60-day extension, then the template should provide a step to inform the Notified Body applicant before the extension starts, that an extension is needed on justified grounds. **Proposed change**: Delete row 4-7 in the Table which refers to supplementary information to be collected from the NB or make it	Partly accepted. It was clarified that these steps are optional in case issues that prevent the adoption of a scientific opinion are identified (*i.e.,* justified grounds).

		clearer in the assessment report template that if information is required in more detail for purposes of consultation than what is provided in draft IFU/SSP, such request should be for the isolated case.	
EMA ASSESSMENT REPORT TEMPLATE Section 2.3	4	**Comment**: Same comment as above	See above.
EMA ASSESSMENT REPORT TEMPLATE Section 3.0	4	**Comment**: The terms should be aligned with what is used in the IVDR. The delivery of EMA is a Scientific Opinion. **Proposed change**: Replace 'Recommendation' with 'Scientific Opinion'.	The Scientific Opinion will be adopted by the CHMP based on the recommendation included in the assessment report and will be a separate document.
EMA ASSESSMENT REPORT TEMPLATE Section 3.0	4	**Comment**: This additional step in the consultation procedure is not foreseen in the IVDR and adds additional complexity, administrative work and potential delays to the process. See also our comment to section 1.2. **Proposed change**: Delete the 3 first paragraphs which refer to supplementary information to be requested or make it clearer in the assessment report template that if information is required in more detail for purposes of consultation than what is provided in draft IFU/SSP, such request should be for the isolated case.	It was clarified in the AR template that these steps are optional in case issues that prevent the adoption of a scientific opinion are identified (*i.e.,* justified grounds). The standard sentences were revised to reflect that the CHMP may issue a **list of questions** to be addressed by the notified body and the CDx manufacturer, as applicable, if further clarification is needed to conclude on the suitability of a CDx for use with the concerned medicinal product(s).
EMA ASSESSMENT REPORT TEMPLATE Section 4.3	4	**Comment:** In the IVDR (line 101), "due consideration" of the scientific opinion should be considered by the Notified Body, but what does that mean?	The notified body should take into consideration the scientific opinion on the suitability of the device in relation to the medicinal product concerned prior to granting the device certification.