CEIVD WG **Comment Form**	Date: May 4, 2026	Document: **Clinical Evidence for IVD Medical Devices – Definitions and Principles of Performance Evaluation**

Name/Organization	Line number	Section	Comments	Proposed change	Resolution
GMTA	General comment		We appreciate the inclusion of Real-World Evidence and Real-World data in this document. In multiple instances, the document comingles these related but distinct concepts, causing potential confusion. We recommend revising the definition for purposes of clarity and to be consistent with broadly accepted definitions.	Use the following language throughout the document: Real-World Evidence (called RWE) is research that uses real-world data (RWD). RWD is collected routinely collected data outside of a traditional clinical study that pertains to someone's health status and health care delivery.	
GMTA	General	General	The term "data" is often incorrectly referred to in a singular vs plural form (e.g., line 599 – "the data is most…)"	Correct throughout the document	
GMTA	General Comment		Risk-based and proportionate application of scientific validity, analytical performance and clinical performance requirements should be consistent with established IMDRF principles and patient safety objectives. Any recommended changes relating to terminology (including use of "clinical evidence") and international concepts (such as "state of the art") are aimed at improving clarity and consistent application of the guidance. Expectations of the evidence necessary to demonstrate safety and performance for the intended use should remain.		
~~GMTA~~	~~47~~	~~Table of Contents~~	~~Defining required reports and documents varies from region to region and implemented per a manufacturer's Quality System. Remove reference to Clinical Evidence Report. In addition, please see our general comment regarding replacing "clinical evidence" with "performance evidence"~~	~~Performance Evidence Documentation~~	

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GMTA	96	2.	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	• ~~the content of the clinical evidence report.~~	
GMTA	101-104	2.	Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices will be reviewed and issued as an IMDRF document. Please reference that document number.	Replace reference with IMDRF CEIVD WG/xxx document number.	
GMTA	105	3.	Sources in the various sections should also be in the reference section.	Include the "Source" documents from sections 4-10 in the 3. References section.	
GMTA	124, 125	4.1	We propose revising to capture an algorithm (for multi-analytes).	"a particular analyte" to "particular analyte(s)"	
GMTA	132	4.2	Suggest modifying the Explanation section of Section 4.2 to include companion diagnostics. Section 4.6 defines Companion Diagnostics; however, this type of device is not included in Section 4.2. Clinical benefit of an IVD medical device".	Add to line 132: ".... or provides information that is essential for the safe and effective use of a therapeutic product".	
GMTA	134, 135	4.3	See general comment above.	Replace "clinical" with "performance"	
GMTA	134-137	4.4	We recommend that the definition for Clinical evidence explicitly include the "clinical benefit" as noted in the EU IVDR, where the device must be safe and perform as intended to achieve the clinical benefit. The current definition, as it is written in this draft, does not capture the need to demonstrate clinical benefit. This addition of "clinical benefit" also aligns with the FDA guidance regarding the topic and the need to provide such evidence.	Definition: Clinical evidence for an IVD medical device is all the information that supports the scientific validity, analytical, and clinical performance of the device, to allow an assessment of whether the device is safe and achieves <u>the intended clinical benefit when used as</u> ~~its intended use as~~ claimed by the manufacturer.	

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GMTA	146	4.5	GHTF/SG5/N8:2012 Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices will be reviewed and issued as an IMDRF document. Please reference that document number.	Replace reference with IMDRF CEIVD WG/xxx document number.	
GMTA	150-170	4	It is recommended that the guidance explicitly emphasise a risk-based and proportionate approach to evidence generation. This foundational principle guides much of current regulation and is a core tenet for many IMDRF members; IVD Clinical Evidence should be no different. Without this clarification, the guidance may be interpreted as requiring the same level of evidence for all IVDs, regardless of risk classification. While many jurisdictions follow a risk-based approach, this principle is not yet universal in all developing regulations. Therefore, the IMDRF is urged to include a statement in the guidance explaining this approach to ensure the final document aligns with the Committee's intentions.	The level and type of evidence required should be proportionate to the device's risk classification and intended use as defined by the manufacturer.	
GMTA	152	4.6	It is important to capture both safety and effectiveness.	"safe or effective" change to safe and effective	
GMTA	157	4.7	We propose revising to incorporate an algorithm analysing a group of markers.	"a target marker" to "target marker(s)"	
GMTA	159-160	4.7	Diagnostic sensitivity may also be reported as 'positive percent agreement'.	(add underlined text): "NOTE 1: Also defined as percent positivity or positive percent agreement in specimens from subjects where the target disease or condition is known to be present."	

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GMTA	150–170	4.6	We recommend that the guidance explicitly emphasize a risk-based and proportionate approach to evidence generation. This foundational principle guides much of current regulation and is a core tenet for many IMDRF members; IVD Clinical Evidence should be no different. Without this clarification, the guidance may be interpreted as requiring the same level of evidence for all IVDs, regardless of risk classification. While many jurisdictions follow a risk-based approach, this principle is not yet universal in all developing regulations. Therefore, we urge the IMDRF to include a statement in the guidance explaining this approach to ensure the final document aligns with the Committee's intentions.	The level and type of evidence required should be proportionate to the device's risk classification and intended use as defined by the manufacturer.	
GMTA	170-171	4.8	Diagnostic specificity may also be reported as 'negative percent agreement'	(add underlined text): "NOTE 1: Also defined as percent negativity or negative percent agreement in specimens from subjects where the target disease or condition is known to be absent."	
GMTA	177	4.9	"purpose" may not be consistent with intent of the document	Remove	
GMTA	200	4.10	"diagnostic, monitoring or compatibility purposes"	diagnostic, monitoring, prognostic or compatibility purposes	
GMTA	201	4.8	Controls, specimen receptacles, instruments and materials from third party manufacturers not intended for IVD use (general purpose) are not considered IVD medical device, and therefore outside of the scope of this document.	Third party controls, specimen receptacles, instruments and materials not intended by that manufacturer (e.g., general purpose) for IVD use should not be included	

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GMTA	214-216	4.11	Our recommended redline is recognized by the EU in the proposed revisions to the EU MDR/IVDR from December 16, 2025, as well as in recent U.S. FDA guidance on RWD.	"Data are typically generated from verification and validation studies (including, where appropriate, clinical performance studies using human specimens) or obtained from literature reviews that confirm the performance of the product. Real-world data, statistical modeling, contrived specimens/simulated clinical matrix, and in silico analysis may also provide supporting evidence."	
GMTA	217-218	4.11	Literature reviews to support performance need to be obtained from systematic reviews (Appendix A)	post-market data (e.g., adverse event reports, post-market surveillance reports, systematic reviews of published literature	
GMTA	250	4.15	The definition is not clear for AI SaIVDs that detect complex morphological patterns without a defined molecular analyte. This is described further in lines 695 through 699 but should be described in the definition of scientific validity of an analyte.	Expand definition to account for pattern-based associations potentially including relevant text from lines 695-699.	
GMTA	266	5	See general comment: The use of the term 'Clinical Evidence' to denote scientific validity, analytical performance, and clinical performance, could be confusing. Clinical evidence could be confused with clinical validation data or clinical real-world data. Also, the use of the term 'clinical evidence' for lower-risk class devices (that might not require clinical validation or clinical performance data) will be particularly confusing.	Change the term 'clinical evidence' to 'performance evidence'.	

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GMTA	267	5	It is stated “Clinical evidence for an IVDR medical device is all the information…” The IVDR definition of “clinical evidence” (Article 2 (36)) includes the clarification “…of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.”	Clarify that in the context of IVD performance evaluation, “clinical evidence” is required to be of a sufficient amount and quality to allow for the qualified assessment of device safety and achievement of the intended clinical benefit.	
GMTA	268	5	See general comment regarding “clinical evidence”	Suggest redefine “Clinical evidence” or replace it with Performance evaluation or performance evidence	
GMTA	288	5	The frequency of an analyte in the population should be added as a factor that influences clinical evidence requirements. Regulators should consider alternate sources of evidence for devices that detect rare analytes.	Add: “the frequency of the analyte in the intended use population”.	
GMTA	273-274	5.	Manufacturing information in and of itself does not contribute to clinical evidence	documentation, device description, labelling, ~~risk analysis and manufacturing information~~, is needed to allow a manufacturer to demonstrate conformity with the	
GMTA	282-283	5.	“Profoundly” indicates that information from IVD medical devices totally influences diagnosis and patient management. More correctly, information from IVD devices may significantly influence diagnosis and patient management.	devices and these decisions can significantly influence diagnosis and patient management	
GMTA	294-297	5	The process of gathering evidence of scientific validity, analytical performance, and clinical performance is defined as ‘Performance Evaluation’. The output of this activity should therefore be called ‘Performance Evidence”.	Change the term ‘clinical evidence’ to ‘performance evidence’.	

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GMTA	300	6	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	Wording in Figure 1 should be replaced with "Performance Evidence Documentation".	
GMTA	302	6	Harmonize terminology and description in two places of document.	Performance evaluation should be regarded as a continuous and iterative process where clinical…	
GMTA	309-311	6	State-of-the-art concept is not an international regulatory approach or methodology; in the interest of harmonization, we would remove this term from the document.	~~The manufacturer should also take into account scientific developments and improvements in the state of the art.~~	
GMTA	327	6	We seek to clarify use of the term "not sufficient" in the sentence.	Add the following text to the end of the sentence "...not sufficient to demonstrate compliance of the device to the applicable essential principles of safety and performance".	
GMTA	347	7.1	It would be helpful to expand upon examples of devices for which it may not be necessary to demonstrate scientific validity.	Clarify that demonstration of scientific validity may not be necessary for devices which have no analyte or marker, and no associated clinical condition or physiological state.	
GMTA	340-341	7.1	Defining required reports and documents varies from region to region and implemented per a manufacturer's Quality System. Remove reference to Clinical Evidence Report.	a brief rationale should be documented ~~in the final clinical evidence report~~ (e.g., a brief list of key references).	
GMTA	381	7.3	State-of-the-art concept is not an international regulatory approach or methodology and we believe should be removed from the guide.	The data or information provided should be of sufficient quality and detail to enable a rational and objective assessment of the scientific validity ~~and should reflect the state of the art~~.	

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GMTA	386	7.3	Defining required reports and documents varies from region to region and implemented per a manufacturer's Quality System. Remove reference to Clinical Evidence Report.	The scientific validity must be documented ~~as part of the clinical evidence report~~.	
GMTA	402	8.1	It is stated that "Analytical performance studies are always required for each IVD medical device." However, there may be IVD medical devices which have no applicable analytical performance characteristics, and thus analytical performance studies would not be applicable.	Clarify that an IVD medical device may have no applicable analytical performance characteristics, and in such cases, analytical performance studies would also not be applicable. Examples: collection devices, specimen receptacles, calibrators, controls, instrumentation,	
GMTA	413	8.1	We suggest to move line 413 above line 412, as accuracy is derived from precision, precision must be cited before accuracy	Move text line 413 before text line 412	
GMTA	419-420	8.1	Specimen stability and device stability are two different concepts and should be separated.	stability of the specimen, device stability using shelf-life, in use, and transport measures	
GMTA	428-431	8.1	Unclear whether the paragraph relates to trueness or whether this recommendation is also for quantitative assay	It is recommended to stipulate whether this is <u>also</u> for quantitative assays <u>in addition to trueness.</u>	
GMTA	436-437	8.1	"In the absence of such approaches, a clinical performance study comparing test performance to the current clinical standard practice would be needed". This may be difficult for novel devices (i.e., where the analyte is not part of the standard practice)	In the absence of such approaches <u>that include a justification</u>	
GMTA	447-448	8.1	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	The analytical performance data must be summarised and documented ~~as part of the clinical evidence report.~~	

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GMTA	450-457	8.2	This section in Document GHTF/SG5/N7:2012 includes more detailed description of Clinical Performance. We recommend incorporating that information in this document as well.	The clinical performance of an IVD medical device may include, but is not limited to: • diagnostic/clinical sensitivity, which indicates the effectiveness of an IVD medical device in correctly classifying patients who have a particular disease or condition • diagnostic/clinical specificity, which indicates the effectiveness of an IVD medical device in correctly classifying patients that do not have a particular disease or condition • positive predictive value, which indicates the effectiveness of an IVD medical device in separating true positive results from false positive results for a given attribute in a given population. negative predictive value, which indicates the effectiveness of an IVD medical device in separating true negative results from false negative results for a given attribute in a given population. The parameters depend on the intended use/purpose of the IVD medical device (diagnosis, screening, classification, therapy selection) and other relevant aspects such as intended use environment/settings (e.g., self-test, point of care) and the	

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				intended user (e.g., qualified healthcare professional, lay person). In addition, we recommend adding the following sentence to the section: The level of evidence required to demonstrate clinical performance should be commensurate with the intended use/purpose and risk classification of the device."	
GMTA	458	8.2	It is stated that "Clinical performance must be demonstrated…unless it is justified by the manufacturer that this is not applicable, for example for certain low-risk IVD medical devices." More specifically, such devices are those which have no applicable clinical performance characteristics and no clinical claims.	Clarify that clinical performance may not be applicable to devices which have no applicable clinical performance characteristics, or clinical claims.	
GMTA	458-465	8.2	Situations where clinical performance would not be expected (GHTF/SG5/N7:2012) are not described in this document, except for low-risk IVD medical devices. Consistent with GHTF/SG5/N7: 2012, we recommend adding explicit reference to assay migration as an example where clinical performance is not needed.	Clinical performance must always be documented. Clinical performance must be demonstrated (using existing and/or newly generated evidence) unless it is justified by the manufacturer that this is not applicable, for example for certain low-risk IVD medical devices, for cases where the same reagents are migrated between instruments with the same basic analytical technology.	

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				Whether the IVD medical device in question is established or novel does not exempt the manufacturer from the requirement to demonstrate clinical performance. However, in case of a novel IVD medical device it is more likely that it is necessary to generate new evidence through a clinical performance study to demonstrate clinical performance.	
GMTA	466-467	8.2	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	The clinical performance data should be documented ~~as part of the clinical evidence report.~~	
GMTA	476	8.2.1	We recommend replacement of "Real-world data/evidence" with the following: "Real-world data". We believe the current description of "Real-world data/evidence" is too narrow and not reflective of standard definitions provided by global regulatory authorities. In addition, the description comingles the separate concepts of real-world data and real-world evidence. It is recommended that the definition focus on real-world data, as the real-world evidence generated from the real-world data, in this context, would be used to support clinical performance.	Real-world data~~/evidence~~: ~~Published experience gained by routine diagnostic testing or the delivery of health care from a variety of sources other than clinical performance studies, pre-and post-market data.~~ Routinely collected data reflecting patient health status and delivery of health care, obtained outside formal clinical performance studies	
GMTA	505-506	8.2.2.1	GHTF/SG5/N8:2012 Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices will be reviewed and issued as an IMDRF document. Please reference that document number.	Replace reference with IMDRF CEIVD WG/xxx document number.	

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GMTA	512-517	8.2.2.2	Narrative literature reviews are established and acceptable methods of literature review and should still be allowable, as described in section 7.1 lines 339-341 regarding scientific validity assessment.	Narrative and systematic literature review can be used to identify published clinical performance data that is not in the possession of the manufacturer that may assist the manufacturer in demonstrating acceptable clinical performance of an IVD medical device. A narrative literature review provide descriptive summaries of topics and may be appropriate to establish scientific validity, and clinical performance data for well-established technologies or low or medium risk IVD medical devices. Systematic reviews aim to provide comprehensive and unbiased summary synthesis of existing evidence on a single topic by using scientific methods to synthesise multiple individual studies in a single place. Use of narrative literature reviews versus systematic literature reviews should be justified and documented.	
GMTA	526 and 527	8.2.2.2	Section 8.2.2.2 seems to use the term “analytic” to describe “analytical” performance. The remainder of the document cites analytical performance in this context.	For consistency and clarity, we recommend using the descriptor “analytical” in this section rather than “analytic”.	
GMTA	573-574	8.2.2.2	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	Once the literature review has been executed, a summary should be prepared and documented ~~included in the clinical evidence report~~.	
GMTA	578-580	8.2.2.3	Defining required reports and documents varies from region to region and implemented per manufacturers Quality System. We advise removing the Reference	The ~~documentation~~ data readily available to the manufacturer ~~for inclusion in the clinical evidence report~~ is likely to be limited to the published paper itself.	

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			to Clinical Evidence Report and instead noting that data needs to be collected in a "document". Keeping it general will allow each jurisdiction to apply this requirement to its own system.		
GMTA	580-613	8.2.2.3	This section refers to real-world data (RWD) and real-world evidence (RWE) as a single term. The interchangeable use of data and evidence creates confusion.	Real-world data (RWD) ~~These types of~~ can be performance data ~~are~~ generated in actual use conditions that are outside the conduct of clinical performance studies. Use of RWD to generate ~~this~~ evidence is part of the lifecycle approach to performance evaluation described above. However, use of real-world ~~data/~~evidence (RWE) alone may not be sufficient to demonstrate clinical performance or extending the intended use/purpose of an IVD medical device. While much of the experience with routine diagnostic testing is found in literature, ~~additional sources of RWD~~ ~~data~~ may include: …. The value of RWE ~~real-world data/evidence~~ is that it provides actual use experience obtained in larger, heterogeneous and more complex populations (e.g., with regard to interfering substances). RWD ~~The data is most~~ can be useful for identifying less common but potentially serious device-related adverse events. RWD can ~~It is~~ also be a particularly useful source of diagnostic testing data for low-risk devices that are based on long standing, well characterized technology and, therefore, unlikely to be the subject of either reporting in the scientific literature or performance study.	

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				The manufacturer should document ~~choose and justify a~~ the methodology for gathering RWD and the a priori protocol (including study design and analytical methods) used to evaluate the relevance and reliability of the ~~appraising~~ real-world ~~data/~~evidence to the regulatory submission. This methodology should be objective so that both favourable and unfavourable data are included. Real-world ~~data/~~evidence may lead to either extension or limitation of the intended use/purpose of an IVD medical device.	
GMTA	593	8.2.2.3	Remove EQA acronym, it is not used elsewhere and upon review of the document, acronyms are scarcely used.	external quality assessment ~~(EQA)~~,	
GMTA	600-601	8.2.2.3	This guide should not suggest or limit the potential usefulness or applications of RWD/E. Please remove this sentence	~~The data is most useful for identifying less common but potentially serious device-related adverse events.~~	
GMTA	604-606	8.2.2.3	Lines 486-488 and Section 8.2.3 already addresses that the data generated should be relevant to the device and considering the advantages and limitations of each data type; and the types of data be documented/ justified. As such we recommend removing the suggested text since it is duplicative and redundant.	~~The manufacturer should choose and justify a methodology for gathering and appraising real-world data/evidence. This methodology should be objective so that both favourable and unfavourable data are included.~~	

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GMTA	625-627	8.2.3	We recommend that this sentence should be deleted or changed to indicate that if a higher weighting is assigned, then a rationale should be provided. There are instances in which real-world data or real-world evidence may be more compelling than clinical performance study data. We seek deletion or a more nuanced approach.	For the purpose of clinical performance evaluation, clinical performance study data is typically weighted higher than literature data and real-world data/evidence." While we prefer the approach above, alternately, consider a sentence similar to the following: <u>In the case where real-world data should be given higher weighting, a rationale for the higher weighting should be provided.</u>	
GMTA	627	8.2.3	Need to clarify the difference between data and evidence.	Revise text "…real-world ~~data/~~evidence."	
GMTA	652	8.2.3	State-of-the-art concept is not an international regulatory approach or methodology and should be struck from the guide.	• ~~state of the art.~~	

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GMTA	661	9.1	To maintain consistency with existing IMDRF guidance, such as N10/12, we recommend the term SaIVD be omitted from the consultation and replaced in its entirety with a term commonly used by IMDRF – SaMD. IMDRF already established on more than one occasion that an IVD can fall under a Medical Device or IVD. For example, N10, Software As a Medical Device: Key Definitions and Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations both state, "SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device". In addition, the established IMDRF approach is already seen implemented in Management Committee Members, such as the European Union. Shifting to a new term that the global community is unfamiliar with risks creating overlap and ambiguity that is unnecessary and can delay innovation.	The terminology (SaIVD) should be replaced with the IMDRF term 'SaMD' and corresponding definitions.	
GMTA	662	9.1	No direct link is provided for linking Software as an IVD to companion diagnostics.	Provide additional context to bridge requirements SaIVD that is intended as a companion diagnostic.	
GMTA	669-671	9.1	The document states that software are typically "subject to more frequent and rapid re-verification throughout the product lifecycle" yet there is no discussion on the flexibility or use of a Predetermined Change Control Plan, which is a precise regulatory mechanism to support the frequent and rapid changes associated with software.	Add in the flexibility and mechanism of a Predetermined Change Control Plan.	
GMTA	675	9.1	Grammatical correction	Change 'is' to 'are': "influence or *are* necessary to an IVD medical device"	

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GMTA	676 & 684	9.1	Section 9.1 states that for AI-based software, the scientific validity and analytical performance of the technology itself may also need to be demonstrated. Requiring manufacturers to establish the scientific validity and analytical performance of an algorithm's architecture (the technology itself) rather than just the clinical association is a significant shift that may lack a clear "ground truth" or established methodology. This challenge could be addressed in line 692 by adding the text in red. See SaIVD/SaMD discussion in earlier comment.	"For some ~~SaIVD,~~SaMD particularly those that employ machine learning or AI algorithms to recognize complex or hidden patterns in datasets, it may be difficult to define or establish appropriate methods for validating scientific validity or certain analytical performance parameters.	
GMTA	712-713	9.1	The document states the "dynamic and adaptive nature of AI algorithms", which seems to imply a continuously learning algorithm that updates their model weights in real-time based on incoming data. It is unclear if this is permissible or how that type of an AI model should be validated.	Provide further details on how a continuously learning algorithm should be modeled or refined in the AI algorithm description. Clear guidance for implementation post-market performance follow-up are needed to ensure correct performance. These can, for example. include elements such as use of real-world evidence, automatic tracking of performance, algorithm-drift analysis and the expected frequency, metrics, and acceptable thresholds.	
GMTA	721	9.1	Reference is made to the human-AI performance concept without a validation framework.	Add guidance on how to evaluate or measure this in a clinical performance study including information on continuous/mandatory training frequencies and interpretable outputs.	

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GMTA	723-725	9.1	"clinical judgement rather than replace it. While AI technology can significantly enhance the interpretative capabilities of IVD medical devices, the final clinical decision must always rest with the qualified healthcare professionals" We recommend that this wording be amended based on the below; AI/ML-enabled devices often support healthcare professional (HCP) decision-making, rather than replace it. However, there may be low-risk situations where it is appropriate for the software to replace HCP decision-making, and indicating that final decisions "must always" rest with qualified healthcare professionals does not consider all potential devices and scenarios (and their associated risks) and is too limiting, particularly as technologies, HCPs, and patients advance.	Delete "must always" in the following sentence: "While AI technology can significantly enhance the interpretative capabilities of IVD medical devices, the final clinical decision ~~must always~~ will often rest with the qualified healthcare professionals.	
GMTA	735	9.2	We recommend using consistency in terms throughout the guidance when possible. Doing so will avoid unnecessary confusion. Specifically, we recommend selecting one term/phrase to refer to "medicinal product/therapy", "therapeutic product", "medicinal product". For example, the term therapeutic product could be used in all three instances.	Suggest using the same term throughout the section to describe medicinal product/therapy", "therapeutic product", "medicinal product".	

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Name/Organization	Line number	Section	Comments	Proposed change	Resolution
GMTA	735-792	9.2	This section indicates that only the pivotal clinical trial for the drug is used for clinical performance for the CDx. However, this is contradictory to EU IVDR as clinical performance from Phase 1, 2, 3, 4 or post-market studies can be used for clinical evidence & clinical performance of the CDx. Any clinical study where a patient decision is made on the basis of the device result (CTA or CDx) is under scope of the EU IVDR.	Clarify all studies e.g., Ph1, 2, 3, 4 or post market studies can be used for establishing clinical performance of CDx.	
GMTA	735-792	9.2	Section indicates that clinical performance of CDx is established by drug-CDx combined studies	Add clarification whether method comparison or accuracy studies can be used to establish clinical performance for CDx	
GMTA	769	9.2	It is possible to bridge to several clinical trial assays or local lab tests (where the result is confirmed by a central lab)	Alternatively, when a clinical trial assay, or where relevant multiple clinical trial assays and/or local laboratory tests, have been used in the clinical development of the medicinal product and in the pivotal clinical trials, a clinical bridging study may be used to establish the clinical performance of a subsequent CDx…	
GMTA	735-807	9.2	The term ‘CDx’ should not be used to describe a clinical trial assay. A CDx is a test that is approved for identifying the individuals who should, or should not, receive a corresponding pharmaceutical therapy. A clinical trial assay is not yet approved for that purpose and therefore should not be referred to as a ‘CDx’.	Use “clinical trial assay” rather than “CDx” when referring to a clinical trial assay throughout Section 9.2	

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GMTA	758-760	9.2	The use of an unapproved diagnostic test in a drug therapy trial does not necessarily signify that the performance of the diagnostic test is also being evaluated in the trial. The test that is used in the trial might not be chosen as the future companion diagnostic; as such, there is no intention to generate performance data in the scope of the therapeutic product trial, no intent to commercialize the test and therefore its use is limited to the pharmaceutical product trial.	Provide additional context to this section to explain that a test can be used in a pharmaceutical product trial without its performance being assessed. For clinical trial assays to be used for a medical purpose in a pharmaceutical trial, there must be evidence of scientific validity and analytical performance. There might also be clinical evidence available for the test. The purpose of the pharmaceutical trial is not necessarily to evaluate the clinical performance of the clinical trial assay unless the same assay is chosen to be the future companion diagnostic for the pharma product.	
GMTA	772	9.2	It should be clarified that not only biomarker positive samples are required for the bridging analysis. In situations where the CTA is being used for therapy selection only, negative samples may not be kept and may have to be procured to support.	The bridging study should establish clinical comparability between the clinical trial assay and the subsequent CDx <u>in the intended use population, by demonstrating concordant classification of both test-positive and test-negative subjects,</u> which can be achieved through provision of direct or indirect comparability data.	

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Name/Organization	Line number	Section	Comments	Proposed change	Resolution
GMTA	772-774	9.2	Section 9.2 states that "The bridging study should establish clinical comparability between the clinical trial assay and the subsequent CDx, which can be achieved through provision of direct or indirect comparability data". To reference a commonly used source which includes accepted methods for CDx, we recommend adding a reference to the 2015 Li publication on bridging studies. Adding the reference may help add appropriate context and improve clarity for regulators and manufacturers.	Suggest adding a superscript reference to the Li 2015 publication (https://pubmed.ncbi.nlm.nih.gov/24897254/) or similar as a source in this section.	
GMTA	808	10	See above comments related to the use of the term 'Clinical evidence'.	Replace the term 'Clinical Evidence' with 'Performance Evidence'.	
GMTA	809	10	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	documentation ~~report~~	
GMTA	811	10	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	The ~~clinical performance~~ evidence documentation ~~report~~ is a compilation of the scientific validity, analytical and clinical performance.	
GMTA	811	10	Defining required reports and documents varies from region to region and implemented per a manufacturers Quality System. Remove reference to Clinical Evidence Report.	The ~~clinical performance~~ evidence documentation ~~report~~ is a compilation of the scientific validity, analytical and clinical performance.	
GMTA	818	10	Harmonize terminology and description in two places of document.	Performance, should be a~~n~~ continuous and iterative process.	
GMTA	824	10	Grammatical correction	Correct 'has' to 'have': "scientific validity and the performance data that have been evaluated"	

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GMTA	863 and 881	Appendix A	For consistency across cited references, list full page numbers for the von Elm and Whiting references that are cited	Line 863: update page range to “344-349” Line 881: update page range to “529-536”	

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