CEIVD WG **Comment Form**	Date: April 6, 2026	Document: **Clinical Evidence for IVD Medical Devices – Definitions and Principles of Performance Evaluation**

Name/Organization	Line number	Section	Comments	Proposed change	Resolution
AdvaMed	General Comment	Entire Document	The term “data” is often incorrectly referred to in a singular versus. plural form (e.g., line 599 - “The data is most...”).	Correct throughout document.	
AdvaMed	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 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.		
AdvaMed	General comment		The use of the term ‘Clinical Evidence’ (which includes evidence of scientific validity, analytical performance, and clinical performance) could be confusing, particularly for lower-risk class devices for which clinical performance data are not required. While we realize that this “clinical evidence” was also used in GHTF/SG5/N6: 2012, which will be superseded upon finalization of this document, we believe that our proposed language promotes the intent of the drafters of the prior version. It is our understanding that the goal of the approach of distinguishing between scientific validity, analytical validity and clinical performance was in fact to underscore that clinical performance does not always need to be demonstrated if the other two are demonstrated. Using terminology other than “clinical” evidence will help clarify this intent.	Consider replacing this term with ‘Performance Evidence’ or similar appropriate terminology that does not use “clinical” throughout the document.	
AdvaMed	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: <u>Real-World Evidence (called RWE) is research that uses real-world data (RWD). RWD are data routinely collected outside of a traditional clinical study that pertains to someone’s health status and health care delivery.</u>	

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AdvaMed	General comment		In approximately a dozen instances, the document refers to “published” literature. However, the use of the word “published” is inconsistent, generating confusion. It appears that in some instances the document may be referring to publicly available; however, the intended meaning is ambiguous. For purposes of clarity and consistency, we recommend removing all references to “published” or “unpublished” literature, and instead simply refer to literature.		
AdvaMed	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. We recognize that IMDRF acknowledges regional differences for document and report requirements. As stated in the IMDRF Table of Contents document: Purpose: To create a comprehensive submission structure that minimizes regional divergences and indicates where regional variation exists.” That being said, for purposes of this particular document, we believe it is best to preserve flexibility. In addition, please see our general comment regarding replacing “clinical evidence” with “performance evidence”.	Performance Evidence Documentation	
AdvaMed	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.~~	
AdvaMed	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.	
AdvaMed	105	3.	Sources in the various sections should also be in the reference section.	Include the “Source” documents from sections 4-10 in the References section.	

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AdvaMed	116-119	3	Given that this document, when finalized, will supersede N6 and N7, it is potentially confusing to reference these superseded documents. For purposes of clarity, we recommend replacing the references to N6 and N7 with the title of this document.	Replace the references to N6 and N7 with the title of this document.	
AdvaMed	124, 125	4.1	We propose revising to capture an algorithm (for multi-analytes).	"a particular analyte" to "particular analyte(s)"	
AdvaMed	127	4.2	We recommend that the definition be updated to add "positive" impact to highlight the value of IVDs to patients and public health. IVDs play an essential role in promoting patient care and public health, and we seek to more fully reflect this value in the document.	Clinical benefit of an IVD medical device Definition: The <u>positive</u> impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a <u>positive</u> impact on patient management or public health.	
AdvaMed	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". While clinical benefits of Companion Diagnostics are detailed in a dedicated section: (9.2 Companion Diagnostics), we also believe a cross reference would be helpful here for purposes of continuity and comprehensiveness.	Add to line 132: ".... or provides information that is essential for the safe and effective use of a therapeutic product (see 9.2).	
AdvaMed	134, 135	4.3	See general comment above	Replace "clinical" with "performance" or similar appropriate terminology that does not use "clinical"	
AdvaMed	134-137	4.4	We recommend that the definition for Clinical evidence explicitly includes 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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AdvaMed	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.	
AdvaMed	152	4.6	It is important to capture both safety and effectiveness.	"safe or effective" change to safe and effective	
AdvaMed	157	4.7	We propose revising to incorporate an algorithm analysing a group of markers.	"a target marker" to "target marker(s)"	
AdvaMed	159-160	4.7	Diagnostic sensitivity may also be reported as '~~positive~~ percent positivity ~~agreement~~'	(add underlined text): "NOTE 1: Also defined as percent positivity in specimens from subjects where the target disease or condition is known to be present. Percent agreement is reported instead of specificity when the true clinical status of a subject is unknown or when the comparator is not a gold standard.	
AdvaMed	150–170	4	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.	

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AdvaMed	170-171	4.8	Diagnostic specificity may also be reported as 'percent negativity ~~percent agreement~~'	"NOTE 1: Also defined as percent negativity in specimens from subjects where the target disease or condition is known to be absent." Percent negativity is reported instead of specificity when the true clinical status of a subject is unknown or when the comparator is not a gold standard.	
AdvaMed	177	4.9	"purpose" may not be consistent with intent of the document	Remove	
AdvaMed	200	4.10	Propose adding "prognostic" to more fully reflect the spectrum of purposes	diagnostic, monitoring, prognostic or compatibility purposes	
	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.	
	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.	
AdvaMed	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	
AdvaMed	250	4.15	The definition is not clear for AI Software as a Medical Device 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.	

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AdvaMed	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'.	
AdvaMed	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.	
AdvaMed	268	5	See general comment regarding "clinical evidence"	Suggest redefine "Clinical evidence" or replace it with Performance evaluation or performance evidence	
AdvaMed	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".	
AdvaMed	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	
AdvaMed	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 ~~profoundly~~ influence diagnosis and patient management	
AdvaMed	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' or similar term that does not use the word "clinical"	

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AdvaMed	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".	
AdvaMed	302	6.	Harmonize terminology and description in two places of document.	Performance evaluation should be regarded as a continuous and iterative process	
AdvaMed	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. As discussed above, we believe it is best to preserve flexibility in this document.	~~The manufacturer should also take into account scientific developments and improvements in the state of the art.~~	
AdvaMed	326	6	The use of the word "generate" in this sentence appears contradictory with the definition of "Generation" provided in line 322, where it states "Generation' refers to production of new evidence...". We therefore recommend an alternate word to be used in this sentence.	However, the manufacturer may not always need to ~~generate~~ provide new evidence....	
AdvaMed	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".	
AdvaMed	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.	
AdvaMed	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).	
AdvaMed	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~~.	
AdvaMed	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~~.	

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AdvaMed	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. Examples include calibrators, controls, instruments, specimen receptacles. We recommend reorganizing this paragraph to first clearly define *analytical performance*. The paragraph should then distinguish between IVDs that meet this definition— for which analytical performance studies are required— and IVDs that do not meet the definition, for which sponsors may provide appropriate justification for alternative approaches to support the intended use.	~~Analytical performance studies are always required for each IVD medical device. The demonstration of analytical performance supports the intended use/purpose of the IVD medical device. Analytical performance is determined by the collection of testing results (analytical performance data) from analytical performance studies used to assess the ability of the IVD medical device to measure a particular analyte~~. Analytical performance is determined by the collection of testing results (analytical performance data) from analytical performance studies used to assess the ability of the IVD medical device to measure a particular analyte. IVDs which meet this definition are required to perform analytical studies to support their intended use/purpose. In certain cases, an IVD (e.g., calibrators, controls, instruments) may not meet the definition of having analytical performance, in those cases adequate justification should be documented to explain why analytical performance is not applicable and by what means the performance of the device for its intended use/purpose of the IVD is determined.	
AdvaMed	404	8.1	We support use of a risk-based approach to analytical performance requirements; it is important to highlight that the level of evidence required in support of analytical performance should be commensurate to the device's intended use/purpose and risk classification. We recommend that this should be described more fully in the text, with concrete examples provided.	IVD medical devices with differing intended uses/purposes and risk classifications will require differing levels of evidence to demonstrate analytical performance. For example, a specimen receptacle may have a differing level of risk, and thus a corresponding differing level of evidence to demonstrate analytical performance, than an assay	
AdvaMed	406	8.1	As discussed above, not all IVD medical devices 'measure a particular analyte, for example specimen management or sample collection devices.	assess the ability of the IVD medical device to ~~measure a particular analyte~~ achieve its intended use/purpose.	

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			The intended use for a specimen receptacle may be to provide the specimen (e.g., serum, plasma, whole blood) for testing but would not be limited to a 'particular analyte'. We recommend rewording this to focus on achieving its intended purpose rather than focusing on the assays.		
AdvaMed	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	
AdvaMed	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.~~	
AdvaMed	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 identifying patients who have a particular disease or condition • ~~and~~ 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 and positive productive value,~~	

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				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. • ~~expected normal and abnormal distributions in test populations.~~ 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 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."	
AdvaMed	458	8.2	As discussed above, we believe this premise is a central one to the document and its predecessor. We propose additional language to strengthen the point that clinical performance may not be applicable to devices which have no applicable clinical performance characteristics, or clinical claims.	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.	

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AdvaMed	458-465		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, 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.	
AdvaMed	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.~~	
AdvaMed	476-478	8.2.1	The definition is not consistent with the current definitions adopted by many regulatory authorities.	Remove “published” from text and revise definition to be consistent with broadly accepted definitions. “Real-World Evidence (called RWE) is research that uses real-world data (RWD). RWD is collected routinely data collected outside of a traditional clinical study that pertains to someone’s health status and health care delivery.”	
AdvaMed	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-	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	

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			world evidence generated from the real-world data, in this context, would be used to support clinical performance.		
AdvaMed	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.	
AdvaMed	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. In addition, see general comment regarding removal of "published"	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 provides 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.	
AdvaMed	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".	
AdvaMed	534-536	8.2.2.2	See general comment	A comprehensive search for peer-reviewed ~~published and unpublished~~ literature and available consensus expert opinions using prospectively defined review criteria. ~~bibliographic databases and grey literature and based on the pre-defined review question~~	

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AdvaMed	540-543	8.2.2.2	Appendix A does not provide additional clarification to the process, and citing journal articles as example methodologies is unconventional approach in IMDRF guides.	the individual study level and using tools developed for this purpose. ~~A variety of quality assessment tools are available according to the type of study/evidence (e.g. randomised controlled trial, test accuracy study). A list of quality assessment tools is provided in Appendix A.~~	
AdvaMed	558-563	8.2.2.2	Delete references to unpublished and grey literature per general comment.	~~The merits and limitations of published and unpublished literature should be considered. Unpublished literature, or grey literature, may not be widely accessible or standardised in terms of format and methodology, however, could be more up to date than published literature and is not affected by publication bias. Likewise, commercial publication is not a guarantee of quality and should not be a pre-requisite for inclusion in a review.~~	
AdvaMed	558-563	8.2.2.2	Remove unpublished and grey literature, and commentary on the utility of these literature types, per general comment.	The merits and limitations of published ~~and unpublished~~ literature should be considered. ~~Unpublished literature, or grey literature, may not be widely accessible or standardised in terms of format and methodology, however, could be more up to date than published literature and is not affected by publication bias. Likewise, commercial publication is not a guarantee of quality and should not be a pre-requisite for inclusion in a review.~~	
AdvaMed	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~~.	
AdvaMed	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~~.	

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AdvaMed	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.	
AdvaMed	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)~~,	
AdvaMed	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.~~	
AdvaMed	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.~~	
AdvaMed	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: In the case where real-world data should be given higher weighting, a rationale for the higher weighting should be provided.	
AdvaMed	627	8.2.3	Need to clarify the difference between data and evidence.	Revise text "…real-world ~~data/~~evidence."	

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Name/Organization	Line number	Section	Comments	Proposed change	Resolution
AdvaMed	643	8.2.3	We recommend that, consistent with a risk-based approach and previous references to conducting a risk-benefit assessment, the device risk classification is an important element to keep in mind when evaluating the clinical performance evidence.	Add as a bullet to the non-exhaustive list of considerations: "- Device risk classification."	
AdvaMed	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.~~	
AdvaMed	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.	
AdvaMed	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.	
AdvaMed	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.	

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Name/Organization	Line number	Section	Comments	Proposed change	Resolution
AdvaMed	675	9.1	Grammatical correction	Change 'is' to 'are': "influence or *are* necessary to an IVD medical device"	
AdvaMed	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.	"For some SaIVD, / 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.	
AdvaMed	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.	
AdvaMed	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.	
AdvaMed	723-725	9.1		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.	

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			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.		
AdvaMed	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".	
AdvaMed	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	
AdvaMed	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.	

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				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.	
AdvaMed	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. See also 16 December 2024 EMA/198592/2022 Rev.1 Guidance on the procedural aspects for the consultation to the European Medicines Agency by a notified body on companion diagnostics A co-developed CDx is a device that is developed in a clinical development program together with the concerned medicinal product, either in view of an initial marketing authorisation or a change of the indication. This can mean that the device was developed in the framework of a pivotal clinical trial with the concerned medicinal product or of a bridging study assessing the concordance of the CDx and the device used in the pivotal clinical trial of the corresponding medicinal product. In case of a bridging study, sufficient documentation needs to be provided to conclude that the performance compares to the device used in the pivotal clinical trial of the corresponding medicinal product and that there is no impact on clinical performance that would be incompatible with the safe and effective use of the medicinal product.	
AdvaMed	808	10	See above comments related to the use of the term 'Clinical evidence'.	Replace the term 'Clinical Evidence' with 'Performance Evidence'.	
AdvaMed	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~~	

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Name/Organization	Line number	Section	Comments	Proposed change	Resolution
AdvaMed	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.	
AdvaMed	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.	
AdvaMed	818	10.	Harmonize terminology and description in two places of document.	performance, should be ~~an~~ continuous and iterative process.	
AdvaMed	824	10	Grammatical correction	Correct 'has' to 'have': "scientific validity and the performance data that have been evaluated"	
AdvaMed	832-919	Appendix A	The text within the Appendix A provides a suggestion on the parameters of conducting literature review, some of which is already covered in section 8.2.2.2 Literature. The additional information in Appendix A does not justify an entire section dedicated to Systematic Literature Reviews and is disproportionate to other important sources of data, such as analytical and performance testing, Real-World Data/Evidence or Software as a medical device, which are significant topic worthy of dedication of an appendix to further elaborate on these crucial topics. Additionally, the inclusion of literature references for more information on the topic is unusual and atypical of IMDRF guidance documents.	Suggest integrated the unique information in Appendix A into Section 8.2.2.2 and eliminated the many cited journal articles or list them in the references, if in fact they are used to create the guidance in 8.2.2.2.	
AdvaMed	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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