



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of comments received on the draft Qualification opinion for Molecule-independent device bridging approach (MIDBA)

Comments from:

Name of organisation or individual
1. SHL Medical
2. Medtech & Pharma Platform Association (MPP)
3. European Federation of Pharmaceutical Industries and Associations (EFPIA)
4. Novo Nordisk A/S
5. A3P TRADE Association
6. Subcutaneous Drug Development and Delivery Consortium

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1. General comments

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
n/a	SHL Medical	<p>The MIDBA should not be limited to one specific platform (i.e., YpsoMate) but should apply to any autoinjector (AI) device or platform that meets the defined criteria proposed by the guidance document.</p> <p><u>Justification:</u></p> <p>Limiting the qualification to a single proprietary platform could undermine fair competition and innovation because many other autoinjectors including the SHL autoinjector platforms (i.e. Molly) share similar specifications (e.g., injection volume, needle length, mechanism of action) and have demonstrated comparable performance in PK and usability studies.</p> <p>Specifically, SHL reviewed the publication Bittner et al. 2025 – “Clinical qualification of subcutaneous injection devices for monoclonal antibodies”. This publication contains an extensive dataset in Table 2 summarizing the PK comparability studies of 29 mAbs where equivalence was established between manual injection (syringe or prefilled syringe) and autoinjector devices. Based on the review of the mAbs, at least 11 of the molecules listed</p>	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>were commercialized in an SHL-manufactured autoinjector, while 8 were launched in a Ypsomed autoinjector. The remaining 10 molecules were either marketed in autoinjectors from other manufacturers or did not reach the market.</p> <p>Therefore, we recommend that the guidance explicitly state that any platform meeting the defined scientific and technical criteria may qualify, regardless of brand.</p>	
n/a	SHL Medical	<p>Physicochemical property similarity to other reference mAbs is not necessary as long as the device and drug meet the defined technical and clinical criteria.</p> <ul style="list-style-type: none"> - Same monoclonal antibody - Same dose and formulation - Same injection volume - Same injection site(s) - An exposed needle length between 4 and 8 mm - Injection volume between 0.5 and 2 mL 	It was not possible to establish a physicochemical design space; therefore, physicochemical similarity to the reference mAbs remains part of the qualification opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
125-126	SHL Medical	<p>The requirement for “slow absorption after SC injection” is not scientifically justified.</p> <p>No specific or measurable parameters have been provided for this criterion,</p> <p>We recommend using injection time (e.g., 5–30 seconds) as a measurable device performance specification instead.</p>	No revision is made. The design space of the MIDBA approach regarding Tmax and injection time has not yet been established.
n/a	SHL Medical	The public review period for this draft guidance should be extended to the first quarter of 2026, as the current timeline coincides with major holiday periods and may limit stakeholders’ ability to provide comprehensive feedback.	A standard review period was applied.
Line 14 (and in Table 2 / line 220)	Medtech & Pharma Platform Association (MPP)	<p>The draft guidance currently limits the context of use to monoclonal antibodies (mAbs). However, the underlying scientific rationale for MIDBA, bridging based on pharmacokinetic comparability and device performance, is equally applicable to other therapeutic protein formats (e.g., bispecific antibodies, multispecific antibodies, single-chain variable fragments (scFv)). Restricting the scope to mAbs only could unnecessarily limit applicability.</p> <p>Proposed change: Modify scope-limiting definitions such as “<i>eligible mAbs</i>” and “<i>monoclonal</i></p>	No revision is made. The opinion is limited to mAbs because the supporting data pertained solely to this class of products.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<i>antibodies</i> " to <i>"therapeutic proteins."</i>	
Line 27	Medtech & Pharma Platform Association (MPP)	<p>The requirement for an absolute injection volume range of 0.5–2 mL appears unnecessarily restrictive. The draft already specifies that the injection volume for the autoinjector must match the volume used in pivotal trials with manual injection (HHS/PFS), which ensures comparability. An additional fixed range could exclude products that otherwise meet all prerequisites. Flexibility within validated device performance ranges would better accommodate diverse product designs.</p> <p>Proposed change: Replace the fixed range with wording that requires the injection volume to be within the validated range for the autoinjector platform, or remove the range entirely, as the <i>"same injection volume"</i> criterion already addresses comparability.</p>	No revision is made; the opinion is limited to the supporting data.
Table 1	Medtech & Pharma Platform Association (MPP)	The phrase "PK characteristic space" is vague and open to interpretation. It is unclear whether this refers to specific PK parameters (e.g., T _{max} , C _{max} , AUC, clearance, half-life, elimination rate constant, volume of distribution). These parameters will naturally vary between molecules and reference mAbs. Without a clear definition, the statement offers	Table 1, which included the phrase in question, has been omitted from the final version of the opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>limited actionable guidance. If intended to focus on Tmax, this is already addressed elsewhere in the document (noting slow absorption with Tmax typically 3–8 days). Greater clarity is needed to avoid ambiguity in regulatory application.</p> <p>Proposed change: Clarify the meaning of “PK characteristic space” and specify which PK parameters are relevant for eligibility (e.g., Tmax only, acknowledging wide inter-subject variability). Alternatively, remove the phrase altogether if no additional value is added.</p>	
Table 1 Line 41	Medtech & Pharma Platform Association (MPP)	<p>A summative human factors study is not required to demonstrate pharmacokinetic comparability. While useful in device usability assessment, it does not provide evidence for PK equivalence. Including it in MIDBA prerequisites may lead to scope confusion. Device usability, while important for overall regulatory submission, should be addressed separately from PK comparability requirements.</p> <p>Proposed change: Remove “summative human factors study for the YpsoMate AI, being successfully completed in a population that reflects the intended use population” for the eligible mAb.</p>	Table 1, which included the requirement in question, has been omitted from the final version of the opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
Line 46-48	Medtech & Pharma Platform Association (MPP)	<p>Not all listed device/formulation attributes (e.g., pH, osmolarity, viscosity, plunger rod length) will necessarily need to match the reference mAb. Some are product-specific and may have negligible impact on PK comparability. For example, plunger rod length is a cosmetic feature and unlikely to influence PK outcomes. Overly rigid requirements could constrain the application of MIDBA unnecessarily.</p> <p>Proposed change: Remove <i>plunger rod length</i> from the list of mAb characteristics to consider. Change statement from "<i>would need to be similar</i>" to "<i>should be considered with respect to the reference mAb(s)</i>."</p>	Reference to the plunger rod length has been removed from the final opinion. A statement has been added at the end of the sentence to support a critical discussion of possible deviations from the reference mAbs.
Line 46-48 (needle depth)	Medtech & Pharma Platform Association (MPP)	<p>Manual injection via syringes often involves needle lengths greater than autoinjectors (e.g., 12.5 mm vs. 4-8 mm). Techniques such as pinching or angled insertion can affect actual delivery depth, and needle movement during injection is possible. Given the variability and lack of precise control in manual injection depth, the essential requirement should be that autoinjector needle length ensures subcutaneous delivery rather than exact matching to manual specifications.</p> <p>Proposed change: Change "<i>needle extension, exposed needle length</i>" to "<i>subcutaneous</i>"</p>	Final opinion was updated to include only exposed needle length.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<i>injection needle,</i> ” ensuring both manual and autoinjector designs deliver to the subcutaneous space. Remove second instance of “ <i>needle length</i> ” in line 48.	
Line 61-65	Medtech & Pharma Platform Association (MPP)	<p>Expecting PK characteristics and formulation properties to be “similar” across eligible mAbs and reference mAbs is overly restrictive. Many PK parameters (e.g., clearance, half-life, volume of distribution) vary inherently between molecules. Similarly, formulation attributes such as excipients and viscosity are product-specific. To avoid unnecessary limitations, eligibility requirements should focus only on attributes with a direct impact on absorption rate and injection performance.</p> <p>Proposed change: Clarify that only attributes directly influencing absorption rate and injection performance are relevant for MIDBA eligibility and require justification.</p>	Clarification added in the final opinion.
Line 115	Medtech & Pharma Platform Association (MPP)	The draft specifies an exposed needle length of 6 mm for the YpsoMate device, while earlier text allows a 4–8 mm range. Citing a single fixed value could unnecessarily restrict flexibility. Given that manual injections provide no precise control over depth, any needle length should be acceptable as long as it achieves subcutaneous delivery.	The reference to 6 mm for the YpsoMate device was removed from the final opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		Proposed change: Clarify that 6 mm is an example specific to YpsoMate and confirm that any length that ensures subcutaneous injection meets MIDBA eligibility. Consider changing statement to: <i>"Based on variability in manual injection, the autoinjector should be designed so that exposed needle length results in subcutaneous delivery."</i>	
Line 132	Medtech & Pharma Platform Association (MPP)	<p>While injection time for HHS/PFS is generally user-dependent and rarely recorded, certain product labels or trial protocols may specify it. For larger-volume HHS injections, transitioning to high-volume autoinjectors should consider maintaining similar administration durations to support MIDBA comparability. This ensures patient usability and potentially mitigates tolerability concerns.</p> <p>Proposed change: Clarify that there is no restriction on the volume of HHS injections which can be considered as long as a comparable injection timeframe is achieved by the autoinjector.</p>	No revision is made; the opinion is limited to the supporting data.
Line 215-216	Medtech & Pharma Platform Association (MPP)	A summative human factors study is not necessary for PK comparability demonstration. While it may form part of a wider drug-device submission, it is unrelated to the PK bridging justification central to MIDBA.	<p>The sentence was removed from the final opinion.</p> <p>A general statement addressing the required provisions at MAA has been included.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		Proposed change: Remove <i>"In addition, a summative human factors study in a population that reflects the intended use population for the eligible mAb will be submitted."</i>	
Lines 11-14	European Federation of Pharmaceutical Industries and Associations (EFPIA)	We welcome this qualification opinion on the molecule-independent device bridging approach (MIDBA) and believe it establishes a valuable precedent for other developers to implement similar technology approaches within product dossiers, in the absence of pursuing separate individual Qualification Opinions or generating additional clinical data. We are also of the opinion that the opinion should be expanded to be agnostic of autoinjector platform technology, as there is no scientific reason to exclude other autoinjector platforms from the scope of the qualification when they meet the eligibility requirements, further detail in the comments provided.	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.
Lines 14-16 Table 1	European Federation of Pharmaceutical Industries and Associations (EFPIA)	It is unclear if the reference products should be omalizumab and gantenerumab, as referenced in the opinion, or products where the company has access to data (either in-house data, mutually agreed access to another company's data, or based on data available in the public domain).	The reference products are omalizumab and gantenerumab. However, in line with the intent of the opinion, products for which the company has access to data may also be used as references to justify modifications to the proposed specifications and/or the AI device.

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		It is recommended to clarify if the company may use publicly available data, should use in-house data, or if data related to omalizumab and gantenerumab will be made available for reference.	
General	Novo Nordisk A/S	<p>General scope: Consider device-agnostic guidance.</p> <p>The context of use is limited to YpsoMate 1.0 mL and 2.25 mL AIs. To maximize public health impact, we recommend EMA consider a phased expansion toward product-agnostic guidance (e.g., other AIs and pens) once sufficient evidence is available, or provide a roadmap describing what additional evidence would be required for broader MIDBA applicability beyond YpsoMate and mAbs. Please also clarify whether, under the same formulation/dose/volume/site conditions, MIDBA principles could support bridging (i) between two autoinjector platforms (AI-to-AI) and (ii) from an autoinjector to a prefilled syringe (AI-to-PFS), and what evidence would be expected in each case.</p>	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification. Alternative bridging scenarios require justification and discussion on a case-by-case basis.
Line 1	A3P TRADE Association	When unable to produce equivalent volume and dose (a requirement) due to fluid loss using the Auto Injector, can an alternate	No revision is made; the opinion is limited to the supporting data. As stated in the opinion changing any of the proposed specifications need to be supported by additional data

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		<p>requirement be made whereby the fluid volume difference (loss) is demonstrated consistently and the volume less the difference equates to equal dose and volume? Position: Relevant to clinical safety and efficacy is the dose, and total volumes are known to be different from PreFilled Syringe and AutoInjector to achieve equivalent dose based on fluid loss in using an Auto-Injector. It may not be feasible to capture equivalent volume and dose in design based on known fluid loss and could result in an actual lower dose delivered. It can be demonstrated the fluid loss is consistent and quantify this amount, and justify the equivalent molar dose is delivered, which may be different than having the same volume and dose in a SC injection by Auto-Injector. Clarify the concentration, and relationship to "overall" injection volume and dose requirement (Ref lines 22-23, 27, and 86-87).</p>	<p>and/or justification.</p>
Line 14-16	A3P TRADE Association	<p>The term "same AI platform" is broad and may lead to inconsistent interpretations. For instance, it could mean the same brand with various customizations or the exact same autoinjector brand and configuration. To avoid ambiguity, it is recommended to define both "same" and "AI platform" explicitly, including</p>	<p>The term AI device is now used in the opinion.</p>

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		any applicable criteria.	
Line 16-17	A3P TRADE Association	To enable broader application of this guidance, we recommend establishing a standardized process for all autoinjector manufacturers to qualify their devices under MIDBA. This process could involve submitting technical comparison data along with a single bridging study using a reference monoclonal antibody. The emphasis should remain on scientific principles and critical delivery attributes such as needle length, injection volume, and injection site. If the slow absorption of mAbs ensures that device differences do not impact pharmacokinetics, then any device meeting these criteria should be eligible for qualification.	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.
Line 26	A3P TRADE Association	The phrase "Slow absorption after SC injection" feels imprecise—"slow" is subjective and could benefit from quantification or clarification. Would it be appropriate to include a bullet addressing viscosity or other formulation-related factors influencing absorption? Alternatively, this may be acceptable given the statement in line 28: "Similar physicochemical properties to at least one reference mAb."	No revision is made; the opinion is limited to the supporting data.
Line 27	A3P TRADE Association	To broaden the application of MIDBA, we propose extending this concept to subcutaneous injection volumes greater than 2	No revision is made; the opinion is limited to the supporting data.

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		<p>mL.</p> <p>Context: Currently, the clinical standard for subcutaneous injections is a maximum 2mL. However, higher volumes have been explored, particularly when delivery time is extended (e.g. with on-body injectors). When the drug formulation, characterization injection site and route of administration are equivalent, the pharmacokinetics are only expected to vary based on individual characteristics (injection site physiology).</p> <p>Proposal:</p> <p>This MIDBA proposal could be expanded to include approved SC injectable mAbs with higher volumes, and potentially other drug types. A controlled flow velocity (CFV; rate) could be introduced to justify larger SC injection volume, as there is currently no defined parameter or requirement for flow rate.)</p>	
Line 41	A3P TRADE Association	Table 1 seems redundant with the bullet points in lines 19–28. To improve clarity and avoid potential inconsistencies, consider removing either the table or the bullet list to streamline readability.	Original Table 1 has been omitted from the final opinion.
Line 42- 45	A3P TRADE	This content is redundant with bullet point	Original Table 1 and other redundancies have been omitted

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	Association	considerations (lines 19-28) and Table 1. Remove or merge into prior content if there is anything unique	from the final opinion.
Line 46-48	A3P TRADE Association	<p>This section is largely redundant with the bullet points (lines 19–28) and Table 1. Additionally, it uses the phrase ‘similar to that’ when describing considerations, whereas the bullet points often use ‘same’ in many cases. Recommend aligning terminology for consistency and removing or consolidating this content if there are no unique elements</p> <p>The term ‘exposed needle length’ may be confusing, as it could be misinterpreted as referring to the syringe’s exposed needle length. Recommend revising the terminology to ‘needle penetration depth’ to better reflect the physiologically relevant parameter.</p> <p>Additionally, the reference to ‘...PK characteristics and formulation properties similar to the ones of the reference mAb(s)...’ appears unclear and potentially inconsistent with earlier bullet points (lines 19–28) and Table 1. Suggest streamlining expectations and presenting them in a single, consistent statement</p>	Original Table 1 and other redundancies have been omitted from the final opinion.
Line 65	A3P TRADE Association	Requiring PK characteristics and formulation properties to be ‘similar’ across eligible mAbs	Clarification added in the final opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>and reference mAbs is overly restrictive. PK parameters (e.g., clearance, half-life, volume of distribution) and formulation attributes (e.g., excipients, viscosity) naturally vary between products. To avoid unnecessary limitations, eligibility criteria should focus only on attributes that directly influence absorption rate and injection performance.</p> <p>Clarify that only attributes impacting absorption rate and injection performance are relevant for MIDBA eligibility and should be justified</p>	
Line 115	A3P TRADE Association	<p>The draft specifies an exposed needle length of 6 mm for the YpsoMate device, while earlier text allows a 4–8 mm range. Referencing a single fixed value could unnecessarily limit flexibility. Since manual injections do not provide precise depth control, any needle length that ensures subcutaneous delivery should be acceptable.</p> <p>Clarify that 6 mm is an example specific to YpsoMate and confirm that any length achieving subcutaneous delivery meets MIDBA eligibility. Suggested wording: 'Based on variability in manual injection, the autoinjector should be designed so that exposed needle length ensures subcutaneous delivery.'</p>	The reference to 6 mm for the YpsoMate device was removed from the final opinion.

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n/a	Subcutaneous Drug Development and Delivery Consortium	<p>The Subcutaneous Drug Development and Delivery Consortium welcomes EMA's intend to qualify the molecule-independent device bridging approach.</p> <p>The Molecule-Independent Device Bridging Approach (MIDBA) represents an important advancement in regulatory science by enabling scientifically justified bridging between delivery devices without molecule-specific pharmacokinetic (PK) comparability studies, when key product and administration criteria are met.</p> <p>This approach has high value in accelerating patient access to innovative, patient-centered delivery solutions. By reducing the need for duplicative and resource-intensive clinical bridging trials in situations where no meaningful PK differences are expected, MIDBA allows developers to introduce improved administration technologies—such as user-friendly autoinjectors—more quickly and efficiently.</p> <p>The framework also promotes optimal resource allocation, focusing development efforts on generating data that address genuine scientific uncertainty and high-impact clinical questions, rather than repeating studies with low probability of yielding clinically relevant new information.</p> <p>Importantly, MIDBA reduces unnecessary clinical burden for participants by minimizing exposure to trials that offer limited opportunity to generate new technical or clinical insights. This aligns with patient-centric development principles, global regulatory efficiency initiatives, and the broader goal of advancing access to biologic therapies delivered in formats</p>	<p>The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification. Alternative bridging scenarios require justification and discussion on a case-by-case basis.</p>

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		<p>that improve convenience, adherence, and quality of life.</p> <p>The draft opinion focuses narrowly on the YpsoMate autoinjector platform. While this reflects the applicant’s submitted data, the scientific rationale underlying MIDBA—reliance on established PK comparability data and validated device performance—is potentially transferable to other autoinjector technologies meeting equivalent technical standards. Limiting qualification to a single device risks duplicating qualification efforts for different platforms with similar design and performance validation. It is therefore recommended to broaden the scope to encompass other autoinjectors, or explicitly state that MIDBA principles can be applied to other devices when supported by comparable justification.</p> <p>-The current framework addresses bridging from manual subcutaneous (SC) injection via prefilled syringe (PFS) to an autoinjector device. However, it does not explicitly consider scenarios involving changes between autoinjector devices, modifications to a previously approved device, or the change from multiple injections to a single injection. To ensure completeness and avoid future ambiguity, the guidance could include an in-scope provision for applying MIDBA when:</p> <ul style="list-style-type: none"> • Transitioning from one autoinjector device to another (whether approved or investigational), with no differences in key, validated parameters • Modifying an original autoinjector design where conditions remain comparable • Consolidating multiple smaller volume injections into a single larger volume 	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		administration (e.g., switching from 2 × 1 mL injections to a single 2 mL injection) where the total volume is unchanged.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
26	SHL Medical	“Slow absorption after SC injection” should not be a required criterion for device bridging. Absorption rate is not determined by the device, and no specific parameters are defined.	No revision is made. The design space of the MIDBA approach regarding Tmax and injection time has not yet been established.
28	SHL Medical	“Similar physicochemical properties to at least one reference mAb” is not necessary; device bridging should be based on technical and clinical criteria, not reference molecule similarity.	No revision is made. In the absence of an established design space, the requirement for reference molecule similarity is maintained.
35–37	SHL Medical	The approach of referring to PK comparability data generated with other mAbs for the same AI platform should be broadened to include any AI platform meeting the defined requirements, not just YpsoMate.	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.
125–126	SHL Medical	The MIDBA draft itself acknowledges that “the design space of the MIDBA approach with respect to Tmax and injection time has not yet been defined.” We recommend using injection time (e.g., 5–30 seconds) as a measurable device performance specification.	No revision is made. The design space of the MIDBA approach regarding Tmax and injection time has not yet been established.
Line 9	European Federation of Pharmaceutical Industries and	Add ‘clinical bridging’ to key words	No revision is made. Clinical bridging has a very broad meaning.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
	Associations (EFPIA)		
Lines 11-14 Lines 19-21 Lines 32-34 Table 2 Lines 218-220 <i>Proposed edits include proposed edits from the next row.</i>	European Federation of Pharmaceutical Industries and Associations (EFPIA)	<p>The draft guidance currently limits the context of use to monoclonal antibodies (mAbs). However, the underlying scientific rationale for MIDBA — bridging based on pharmacokinetic comparability and device performance — is equally applicable to other molecules (therapeutic protein formats (e.g., bispecific antibodies, multispecific antibodies, single-chain variable fragments (scFv)), biologics, small molecules with adequately long tmax). Restricting the scope to mAbs only could unnecessarily limit applicability.</p> <p>Recommendation: Modify scope-limiting definitions such as “eligible mAbs” and “monoclonal antibodies” to “therapeutic proteins.” Some proposed edits are provided below, but are not inclusive of all changes required.</p> <p>Proposed edit (Lines 11-14): <i>The molecule-independent device bridging approach (MIDBA) is qualified as an alternative methodology for clinical bridging from manual subcutaneous (SC) injection via a handheld</i></p>	No revision is made. The opinion is limited to mAbs because the supporting data pertained solely to this class of products.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p><i>syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform for therapeutic proteins.</i></p> <p>Proposed edit (lines 19-21): <i>The following conditions need to be fulfilled to accept MIDBA for device bridging for therapeutic proteins from manual (HHS/PFS) to automated SC injection using a platform autoinjector:</i></p> <ul style="list-style-type: none"> • <i>Same therapeutic protein</i> <p>Proposed edit (lines 32-34): <i>The molecule-independent device bridging approach (MIDBA) is proposed as an approach to support bridging from manual subcutaneous (SC) injection via a handheld syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform for therapeutic proteins without additional clinical data.</i></p> <p>Proposed edit (Table 2): Therapeutic protein³</p> <p>Proposed edit (lines 218-220): <i>This approach is endorsed and assumes that analytical comparability and formulation characterization, design verification and</i></p>	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p><i>validation, including the human factors study, for the platform AI will be successfully conducted for the eligible therapeutic protein.</i></p>	
<p>Lines 11-14 Lines 19-20 Lines 32-34 Lines 218-220</p> <p><i>Proposed edits include proposed edits from the previous row.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>EMA should note that other companies use different suppliers for PFS and prefilled pens (both autoinjectors at 1.0 mL and 2.25 mL for mAb products, and pen injectors of other products) that have the same or similar technological characteristics (i.e., are platform devices). The MIDBA method should apply to other autoinjector platforms with a similar mechanism of action (e.g., spring-loaded injection).</p> <p>It is recommended to broaden the scope of autoinjectors from “YpsoMate 2.25 and 1.0 AIs” to “platform autoinjectors”. The requirements that the devices is the same as in the reference product and PK comparability data has been generated would still apply.</p> <p>Proposed edit (Lines 11-14): <i>The molecule-independent device bridging approach (MIDBA) is qualified as an alternative methodology for clinical bridging from manual subcutaneous (SC) injection via a handheld</i></p>	<p>The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p><i>syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform for therapeutic proteins.</i></p> <p>Proposed edit (lines 19-20): <i>The following conditions need to be fulfilled to accept MIDBA for device bridging for therapeutic proteins from manual (HHS/PFS) to automated SC injection using a platform autoinjector:</i></p> <p>Proposed edit (lines 32-34): <i>The molecule-independent device bridging approach (MIDBA) is proposed as an approach to support bridging from manual subcutaneous (SC) injection via a handheld syringe (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform for therapeutic proteins without additional clinical data.</i></p> <p>Proposed edit (lines 218-220): <i>This approach is endorsed and assumes that analytical comparability and formulation characterization, design verification and validation, including the human factors study, for the platform AI will be successfully conducted for the eligible therapeutic</i></p>	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<i>protein.</i>	
Line 27	European Federation of Pharmaceutical Industries and Associations (EFPIA)	<p>The requirement for an absolute injection volume range of 0.5–2 mL appears unnecessarily restrictive. The draft already specifies that the injection volume for the autoinjector must match the volume used in pivotal trials with manual injection (HHS/PFS), which ensures comparability. An additional fixed range could exclude products that otherwise meet all prerequisites. Flexibility within validated device performance ranges would better accommodate diverse product designs.</p> <p>Recommendation: Replace the fixed range with wording that requires the injection volume to be within the validated range for the autoinjector platform, or remove the range entirely, as the “same injection volume” criterion already addresses comparability.</p> <p>Proposed edit: <i>Injection volume</i> <i>between 0.5 and 2 mL</i> <i>within the validated range for the autoinjector platform</i></p>	No revision is made; the opinion is limited to the supporting data.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
<p>Line 41 / Table 1</p> <p><i>Proposed edits include proposed edits from other rows.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>The phrase “PK characteristic space” is vague and open to interpretation. It is unclear whether this refers to specific PK parameters (e.g., Tmax, Cmax, AUC, clearance, half-life, elimination rate constant, volume of distribution). These parameters will naturally vary between molecules and reference mAbs. Without a clear definition, the statement offers limited actionable guidance. If intended to focus on Tmax, this is already addressed elsewhere in the document (noting slow absorption with Tmax typically 3–8 days). Greater clarity is needed to avoid ambiguity in regulatory application.</p> <p>Recommendation: Clarify the meaning of “PK characteristic space” and specify which PK parameters are relevant for eligibility (e.g., Tmax only, acknowledging wide inter-subject variability). Alternatively, remove the phrase altogether if no additional value is added.</p> <p>Proposed edit: <i>Assessment of eligible therapeutic protein’s PK characteristics space (i.e., attributes directly influencing absorption rate and injection performance) based on proposed reference therapeutic protein and</i></p>	<p>Original Table 1 has been omitted from the final opinion.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		therapeutic protein-platform AI device combination products in the public domain.	
Line 41 / Table 1 <i>Proposed edits include proposed edits from other rows.</i>	European Federation of Pharmaceutical Industries and Associations (EFPIA)	<p>Clinical bridging has been demonstrated for the same total volume but a different number of injections (e.g., omalizumab (two 1mL injections with a PFS to one 2mL injection with an autoinjector or PFS) and secukinumab (two 1mL injections with a PFS to one 2mL injection with a PFS). This should also be considered as acceptable in the MIDBA.</p> <p>Proposed edit: Therapeutic protein / platform AI bridge: <i>The same total dose volume is administered with the AI and the HHS/PFS at the same injection site.</i></p>	Original Table 1 has been omitted from the final opinion. Nevertheless, the opinion is limited to the supporting data.
Line 41 / Table 1 Lines 215-216 <i>Proposed edits include proposed edits from other rows.</i>	European Federation of Pharmaceutical Industries and Associations (EFPIA)	A complete design verification and validation technical package is not provided in MAA applications for Autoinjectors, as these are single integral drug-device combinations subject to Art. 117 MDR requirements i.e., a NBOp is obtained and the NBOp report is submitted in the MAA. Therefore, EMA will only receive the NBOp report but not the technical package. Additionally, a summative human factors study is not required to demonstrate PK comparability. While useful in device usability	<p>The related text was removed from the final opinion.</p> <p>A general statement addressing the required provisions at MAA has been included.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>assessment, it does not provide evidence for PK equivalence. Including it in MIDBA prerequisites may lead to scope confusion. Device usability, while important for overall regulatory submission, should be addressed separately from PK comparability requirements.</p> <p>Recommendation: Remove “summative human factors study for the YpsoMate AI, being successfully completed in a population that reflects the intended use population” for the eligible mAb.</p> <p>Proposed edit (Table 1): <i>Analytical comparability and formulation characterization, design verification and validation for the eligible therapeutic protein.</i></p> <p>Proposed edit (Lines 214-217): <i>In future marketing authorisation applications with a platform AI drug delivery device, a complete design verification and validation technical package will be reflected in the Notified Body Opinion Report as per Article 117 of the Medical Device Regulation (EU) 2017/745.</i></p>	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p><i>This approach is endorsed and assumes that analytical comparability and formulation characterization, design verification and validation for the platform AI will be successfully conducted for the eligible therapeutic protein.</i></p> <p><i>Alignment with the requirements in the CHMP Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) is expected, unless thoroughly justified.</i></p>	
<p>Lines 46-48</p> <p><i>Proposed edits include proposed edits from other rows.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>Not all listed device/formulation attributes (e.g., pH, osmolarity, viscosity, plunger rod length) will necessarily need to match the reference mAb. Some are product-specific and may have negligible impact on PK comparability. For example, plunger rod length is a cosmetic feature and unlikely to influence PK outcomes. Overly rigid requirements could constrain the application of MIDBA unnecessarily.</p> <p>Recommendation: Remove plunger rod length from the list of mAb characteristics to consider. Change statement from “would need to be similar” to “should be considered with respect to the reference therapeutic protein.”</p>	<p>Redundant text was removed from the final qualification opinion. Text is further clarified in the scientific discussion to reflect the comments.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>Proposed edit: <i>In this scenario, device and formulation properties such as needle extension, exposed needle length, product formulation, osmolarity, pH, injection rate, volume and time, viscosity, needle length should be considered with respect to the reference therapeutic protein.</i></p>	
<p>Lines 46-48</p> <p><i>Proposed edits include proposed edits from other rows.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>Manual injection via syringes often involves needle lengths greater than autoinjectors (e.g., 12.5 mm vs. 4–8 mm). Techniques such as pinching or angled insertion can affect actual delivery depth, and needle movement during injection is possible. Given the variability and lack of precise control in manual injection depth, the essential requirement should be that autoinjector needle length ensures subcutaneous delivery rather than exact matching to manual specifications.</p> <p>Recommendation: Change “needle extension, exposed needle length” to “subcutaneous injection needle,” ensuring both manual and autoinjector designs deliver to the subcutaneous space. Remove second instance of “needle length” in line 48.</p>	<p>Redundant text was removed from the final qualification opinion. Text is clarified in the scientific discussion to reflect the comments.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>Proposed edit: <i>In this scenario, device and formulation properties such as subcutaneous injection needle, product formulation, osmolarity, pH, injection rate, volume and time, viscosity would need to be similar to that of the reference therapeutic protein.</i></p>	
<p>Lines 56-58</p> <p><i>Proposed edits include proposed edits from other rows.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>Comparable PK between injection sites can be demonstrated in clinical trials other than pivotal clinical trials. Additionally, clinical practice is the rotation principle between thigh, abdomen, and upper arm.</p> <p>Recommendation: Add text allowing other studies to substantiate injection sites as below.</p> <p>Proposed edit: <i>Considering the observed injection-site-dependent PK for a number of mAbs, the Applicant proposes that only injection sites previously qualified with manual injection via HHS/PFS (abdomen, upper arm or thigh) in pivotal clinical trials or other clinical pharmacology studies evaluating injection sites for the proposed therapeutic protein would be eligible for use with the platform AI.</i></p>	<p>Text is clarified in the scientific discussion to reflect the comments.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
<p>Lines 61-65</p> <p><i>Proposed edits include proposed edits from other rows.</i></p>	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>Expecting PK characteristics and formulation properties to be “similar” across eligible mAbs and reference mAbs is overly restrictive. Many PK parameters (e.g., clearance, half-life, volume of distribution) vary inherently between molecules. Similarly, formulation attributes such as excipients and viscosity are product-specific. To avoid unnecessary limitations, eligibility requirements should focus only on attributes with a direct impact on absorption rate and injection performance.</p> <p>Recommendation: Clarify that only attributes directly influencing absorption rate and injection performance are relevant for MIDBA eligibility and require justification.</p> <p>Proposed edit: <i>The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties similar to the ones of the reference therapeutic protein(s), where in vivo data are available (isotype, injection volume, concentration, injection time, formulation ingredients, bioavailability values, Tmax values). However, the Applicant was not able to define a “design space” as asked, and there are no actual limits defined for these</i></p>	<p>Text is clarified in the scientific discussion to reflect the comments.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p><i>parameters. Therefore, any deviation from the value of the reference therapeutic protein(s) needs to be thoroughly justified, where attributes directly influence absorption rate and injection performance.</i></p>	
Line 114-115	<p>European Federation of Pharmaceutical Industries and Associations (EFPIA)</p>	<p>The draft specifies an exposed needle length of 6 mm for the YpsoMate device, while earlier text allows a 4–8 mm range. Citing a single fixed value could unnecessarily restrict flexibility. Given that manual injections provide no precise control over depth, any needle length should be acceptable as long as it achieves subcutaneous delivery.</p> <p>Recommendation: Clarify that 6 mm is an example specific to YpsoMate and confirm that any length that ensures subcutaneous injection meets MIDBA eligibility. Consider changing statement to: “Based on variability in manual injection, the autoinjector should be designed so that exposed needle length results in subcutaneous delivery.”</p> <p>Proposed edit: <i>Based on variability in manual injection, the autoinjector should be designed so that exposed needle length results in</i></p>	<p>The reference to 6 mm for the YpsoMate device was removed from the final opinion.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<i>subcutaneous delivery. This can be endorsed by the CHMP.</i>	
Line 131-134	European Federation of Pharmaceutical Industries and Associations (EFPIA)	<p>While injection time for HHS/PFS is generally user-dependent and rarely recorded, certain product labels or trial protocols may specify it. For larger-volume HHS injections, transitioning to high-volume autoinjectors should consider maintaining similar administration durations to support MIDBA comparability. This ensures patient usability and potentially mitigates tolerability concerns.</p> <p>Recommendation: Clarify that there is no restriction on the volume of HHS injections which can be considered as long as a comparable injection timeframe is achieved by the autoinjector.</p> <p>Proposed edit: <i>The Applicant points out that for an HHS/PFS, the injection time is not tested because it is user dependent. The injection time is also rarely recorded in clinical studies, but it will inevitably be variable for manual injections due to individual user preferences and capabilities.</i> <i>There is no restriction on the volume of HHS injections which can be considered</i></p>	No revision is made; the opinion is limited to the supporting data.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<i>as long as a comparable injection timeframe is achieved by the autoinjector.</i>	
Lines 59-74	Novo Nordisk A/S	<p>Clarify applicability beyond the two reference mAbs and define suitability characteristics</p> <p>We note reliance on PK comparability data for omalizumab and gantenerumab as references. Within the current scope (monoclonal antibodies administered via Ypsomate 1.0 mL and 2.25 mL), please clarify whether the proposed “design space” informed by these references is intended to apply to all eligible molecules that meet the stated prerequisites, and specify criteria to determine when a candidate is “similar” enough to use MIDBA without molecule-specific PK bridging.</p>	In the absence of a well-defined design space, it is difficult to provide more detailed criteria than the ones provided in the opinion.
Lines 20-28 125-134	Novo Nordisk A/S	<p>The draft refers to “slow absorption” without quantitative thresholds.</p> <p>We request nonbinding, indicative ranges for key PK parameters (e.g., median Tmax, acceptable variability) and a decision framework for case-by-case justification when parameters deviate from the reference profile.</p>	In the absence of a well-defined design space, it is difficult to provide more detailed criteria than the ones provided in the opinion.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
Lines 86-97 192-211	Novo Nordisk A/S	<p>Provide a decision framework for "clinical gaps".</p> <p>The draft implies that, with the same mAb, dose, formulation, volume, and qualified sites, molecule-specific PK and local tolerability studies may be omitted with justification. We request a structured decision framework describing what constitutes a "clinical gap," the minimum evidence to address it (e.g., HF outcomes, bench data), and triggers for when additional clinical assessment would be required. Please also confirm that MIDBA can remain the regulatory foundation when a limited parameter differs (e.g., AI 0.4 mL vs mPFS 0.5 mL of the same dose/formulation), provided targeted supportive data justify no meaningful impact on PK or local tolerability.</p>	No revision is made; A decision framework for 'clinical gaps' was not discussed or supported by the data provided in this qualification procedure.
Lines 101-115	Novo Nordisk A/S	<p>Address broader user populations for IM risk.</p> <p>The needle-length constraint (exposed 4–8 mm) is presented with a focus on limb injections, males, and BMI <25 kg/m². Please clarify expectations for other user populations (e.g., pediatric, elderly, lean/muscular subjects) and whether labeling, human factors, and bench verification should explicitly cover</p>	No revision is made; The MIDBA approach in other user populations was not discussed or supported by the data provided in this qualification procedure.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		these groups to ensure consistent subcutaneous delivery.	
Lines 138-158	Novo Nordisk A/S	<p>Increase transparency on the validation set “Support from an expanded validation set” is described qualitatively.</p> <p>Please disclose, at least in summary form, the datasets, inclusion/exclusion criteria, devices used, and key outcomes (e.g., ranges of Tmax, BE conclusions), or specify how sponsors can access sufficient details to rely on these data in regulatory justifications.</p>	EMA qualification is subject to CCI provisions.
Line 81 Table 2	Novo Nordisk A/S	<p>Define “Control strategy” and refine footnotes.</p> <p>The first four parameters in Table 2 are addressed by “Control strategy.” Please clarify whether this refers to pharmaceutical quality control strategy, device design control, or both, and refine footnotes to specify scope (e.g., excipient quality/quantity, manufacturing tolerances affecting delivery dynamics) to support consistent application across submissions.</p>	No revision is made; we consider the current information adequate.
Line 11-18	Subcutaneous	General applicability	The qualification opinion has been extended to encompass

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
	Drug Development and Delivery Consortium	<p>The MIDBA approach should be applicable to demonstration of comparability to any conforming AI platform.</p> <p>Proposed change: The molecule-independent device bridging approach (MIDBA) is qualified as an alternative methodology for clinical bridging from manual subcutaneous (SC) injection via a handheld syringe 12 (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform (specifically for example, the YpsoMate 2.25 and 1.0 AIs) for monoclonal antibodies (mAbs). With the MIDBA, it is proposed that individual clinical device qualification for mAbs using the YpsoMate or conforming AI platform is replaced by referring to available PK comparability data generated with other mAbs for the same YpsoMate or conforming AI platform. This approach would omit the need to generate molecule-specific PK comparability assessments for new mAbs using the YpsoMate or conforming AI platform."</p>	other AI devices, contingent upon the submission of adequate supporting data and/or justification.
Line 46-48	Subcutaneous Drug Development and Delivery	Not all listed device/formulation attributes (e.g., pH, osmolarity, viscosity, plunger rod length) will necessarily need to match the reference mAb. Some are product-specific and may have negligible impact on PK	Redundancies were removed. Text was modified accordingly.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
	Consortium	<p>comparability. For example, plunger rod length is a technical feature and unlikely to influence PK outcomes. Injection volume is explicitly mentioned and directly drives plunger rod length, which may make this parameter redundant.</p> <p>Overly rigid requirements could constrain the application of MIDBA unnecessarily.</p> <p>Proposed change: Remove plunger rod length from the list of mAb characteristics to consider. Change statement from “would need to be similar” to “should be considered with respect to the reference mAb(s).”</p>	
Line 46-48	Subcutaneous Drug Development and Delivery Consortium	<p>Manual injection via syringes often involves needle lengths greater than autoinjectors (e.g., 12.5 mm vs. 4–8 mm). Techniques such as pinching or angled insertion can affect actual delivery depth, and needle movement during injection is possible. Given the variability and lack of precise control in manual injection depth, the essential requirement should be that autoinjector needle length ensures subcutaneous delivery rather than exact matching to manual specifications.</p> <p>Proposed change: injection needle,” ensuring both manual and autoinjector designs deliver</p>	Redundancies were removed. Text was modified accordingly.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		to the subcutaneous space. Remove second instance of "needle length" in line 48.	
Line 61-65	Subcutaneous Drug Development and Delivery Consortium	<p>Expecting PK characteristics and formulation properties to be "similar" across eligible mAbs and reference mAbs is overly restrictive. Many PK parameters (e.g., clearance, half-life, volume of distribution) vary inherently between molecules. Similarly, formulation attributes such as excipients and viscosity are product-specific. To avoid unnecessary limitations, eligibility requirements should focus only on attributes with a direct impact on absorption rate and injection performance.</p> <p>Proposed change: Clarify that only attributes directly influencing absorption rate and injection performance are relevant for MIDBA eligibility and require justification.</p>	Text was modified accordingly.
Line 20	Subcutaneous Drug Development and Delivery Consortium	<p>An autoinjector which shares the same or similar delivery profile as the Ypsomate devices can be considered equivalent to hand held syringes/Pre filled syringes and also equivalent to the Ypsomate devices.</p> <p>Primary literature reference (Bittner et al, 2025) draws from a database of numerous drugs delivered by various autoinjectors supporting this justification. It is not limited to</p>	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>the Ypsomate 1 and 2.25 mL devices.</p> <p>Rationale: This change is in alignment with the Medical Device Regulation ((EU) 2017/745) requirements regarding “state of the art”. (defined in IMDRF Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices section 3.43.</p> <p>Proposed change: Add the statement “Conditions for MIDBA for device bridging from manual to automated SC injection may be fulfilled by any Autoinjector which conforms to the exposed needle length (between 4-8mm) requirements.”</p>	
Table on line 81	Subcutaneous Drug Development and Delivery Consortium	The defined injection depth between 4 and 8 mg is well chosen and indeed prevents i.m. injection.	n/a
Line 35-37	Subcutaneous Drug Development and Delivery Consortium	<p>With the MIDBA, it is proposed that individual clinical device qualification for mAbs using the YpsoMate AI platform is replaced by referring to available PK comparability data generated with other mAbs for the same AI platform</p> <p>The data presented supports all autoinjectors meeting the criteria of 4-8 mm and injection</p>	The qualification opinion has been extended to encompass other AI devices, contingent upon the submission of adequate supporting data and/or justification.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>volume of 0.5-2mL. There have been no functional parameters unique to the Ypsomate devices presented in this document that would warrant their exclusivity for the MIDBA approach. The primary literature reference includes 29 PK studies using injection devices that demonstrated PK comparability, however the Ypsomate device are only cited in 2 of those studies (omalizumab and gantenerumab). This suggests that there is a much broader utility of the MIDBA approach.</p> <p>The term "same AI platform" is broad and may lead to inconsistent interpretations. For instance, it could mean the same brand with various customizations or the exact same autoinjector brand and configuration. To avoid ambiguity, it is recommended to define both "same" and "AI platform" explicitly, including any applicable criteria.</p> <p>Note: If certain design differences in the autoinjector component are acceptable, the critical design features that must remain unchanged between the autoinjector used in reference PK comparability studies and the autoinjector proposed for market approval should be clearly specified.</p>	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>To enable broader application of this guidance, we recommend establishing a standardized process for all autoinjector manufacturers to qualify their devices under MIDBA. This process could involve submitting technical comparison data along with a single bridging study using a reference monoclonal antibody. The emphasis should remain on scientific principles and critical delivery attributes such as needle length, injection volume, and injection site. If the slow absorption of mAbs ensures that device differences do not impact pharmacokinetics, then any device meeting these criteria should be eligible for qualification.</p> <p>Proposed change: “With the MIDBA, it is proposed that individual clinical device qualification for mAbs using the YpsoMate or conforming AI platform is replaced by referring to available PK comparability data generated with other therapeutic proteins or other biologic modalities.</p>	
Line 24	Subcutaneous Drug Development and Delivery	Regarding the conditions that need to be fulfilled to accept MIDBA for device bridging for monoclonal antibodies from manual (HHS/PFS), it must be acknowledged that for most of the marketed mAbs a free choice of	No revision is made; the opinion is limited to the supporting data.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
	Consortium	<p>injections site, i.e., upper shoulder, abdominal region or thigh, has been approved. Even in case of an impact of injection site, it can be argued that exposure differences of approximately up to 15% are not clinically significant from a clinical efficacy or safety point of view.</p> <p>Proposed change:</p> <p>It would be welcomed to have guidance to strengthen site-specific requirements on BMI/sex/site risk assessment for SC depth vs. IM risk.</p>	
Line 14, Table 2, Line 220	Subcutaneous Drug Development and Delivery Consortium	<p>Other biologics/therapeutic proteins/modalities</p> <p>Comment:</p> <p>The draft guidance currently limits the context of use to monoclonal antibodies (mAbs). However, the underlying scientific rationale for MIDBA — bridging based on pharmacokinetic comparability and device performance — is equally applicable to other therapeutic protein formats (e.g., bispecific antibodies, multispecific antibodies, single-chain variable fragments (scFv)). Restricting the scope to mAbs only could unnecessarily limit</p>	No revision is made. The opinion is limited to mAbs because the supporting data pertained solely to this class of products.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>applicability.</p> <p>Proposed change: Modify scope-limiting definitions such as "eligible mAbs" and "monoclonal antibodies" to "therapeutic proteins."</p>	
Table 2 (final row)	Subcutaneous Drug Development and Delivery Consortium	<p>Further define "Design Space."</p> <p>Proposed change: Providing numeric definitions (e.g., Tmax range 2–13 or 3–8 days) and related parameters (e.g., similar viscosity, similar injection rate) could be helpful.</p>	In the absence of a well-defined design space, it is difficult to provide more detailed criteria than the ones provided in the opinion.
Line 28	Subcutaneous Drug Development and Delivery Consortium	<p>Define "similar" physicochemical properties.</p> <p>Proposed change: Quantitative criteria (e.g., MW, similar viscosity, similar excipients) and validation rationale for reference mAbs would be helpful.</p>	In the absence of a well-defined design space, it is difficult to provide more detailed criteria than the ones provided in the opinion.
Table 1, Line 214-217	Subcutaneous Drug Development and Delivery Consortium	<p>Other studies needed for MIDBA</p> <p>Comment: A summative human factors study is not required to demonstrate pharmacokinetic comparability. While useful in device usability assessment, it does not provide evidence for PK comparability or bioequivalence. Including</p>	<p>The related text was removed from the final opinion.</p> <p>A general statement addressing the required provisions at MAA has been included.</p>

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>it in MIDBA prerequisites may lead to scope confusion. Device usability, while important for overall regulatory submission, should be addressed separately from PK comparability requirements.</p> <p>Design Verification, excluding exposed needle length and delivered volume, and validation, including human factors studies, are assumed to be independent of MIDBA approach.</p> <p>Further, a complete design verification and validation technical package is not provided in MAA applications for Autoinjectors, as these are single integral drug-device combinations subject to Art. 117 MDR requirements, i.e., we need a NBOP for this. Therefore, EMA will only receive the NBOP Report but not the technical package. This should be amended accordingly.</p> <p>Proposed change:</p> <p>Remove “summative human factors study for the YpsoMate AI, being successfully completed in a population that reflects the intended use population” for the eligible mAb”.</p>	
Line 214-220	Subcutaneous Drug Development	<p>Knowing that</p> <p>- IEC62366-1:2020 proposes alternative to summative study (part 5.9): ‘For SUMMATIVE</p>	A general statement addressing the required provisions at MAA has been included.

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
	and Delivery Consortium	<p>EVALUATION, the MANUFACTURER may use data obtained from the SUMMATIVE EVALUATIONS of products with an equivalent USER INTERFACE together with a technical rationale for how this data is applicable. The results shall be stored in the USABILITY ENGINEERING FILE.'</p> <ul style="list-style-type: none"> - AI may already be approved on the European market for similar applications, - Device manufacturers may have HF data for the AI which can be shared with pharmaceutical companies, <p>Alternative to summative study could be accepted as per some conditions as proposed:</p> <p>Proposed change:</p> <p>For future marketing authorisation applications with AI devices for mAbs, a comprehensive design verification and validation technical package will be included. The need for a summative human factors study should be determined based on a risk-based gap analysis of existing usability evidence.</p> <p>If data from previous summative evaluations of products with an equivalent user interface, combined with a technical rationale,</p>	

Line number(s) of the relevant text	Stakeholder number	General comment	Outcome
		<p>demonstrate that usability requirements are met for the intended use population (or a 'worst case scenario' population identified & justified), a thorough risk-based justification may be provided instead of conducting a new summative study.</p> <p>A summative human factors study should only be performed if the gap analysis identifies residual usability risks that cannot be mitigated through existing evidence and rationale. All supporting data, rationale, and conclusions will be documented in the Usability Engineering File in accordance with IEC 62366-1 2020.</p>	