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SCIENCE MEDICINES HEALTH

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3 Committee for Medicinal Products for Human Use (CHMP)

4 **Draft qualification opinion for molecule-independent**
5 **device bridging approach (MIDBA)**
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Draft agreed by Scientific Advice Working Party (SAWP)	05 June 2025
Adopted by CHMP for release for consultation	18 September 2025 ¹
Start of public consultation	24 October 2025 ²
End of consultation (deadline for comments)	19 December 2025

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Comments should be provided using this [template](#). The completed comments form should be sent to ScientificAdvice@ema.europa.eu

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Keywords	YpsoMate 2.25 and 1.0 autoinjector, PK comparability, Monoclonal Antibodies
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¹ Last day of relevant committee meeting

² Date of publication on the EMA public website



Qualification Opinion

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 (HHS) or prefilled syringe (PFS) to an autoinjector (AI) platform (specifically 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 AI platform is replaced by referring to available PK comparability data generated with other mAbs for the same AI platform. This approach would omit the need to generate molecule-specific PK comparability assessments for new mAbs using the YpsoMate AI.

The following conditions need to be fulfilled to accept MIDBA for device bridging for monoclonal antibodies from manual (HHS/PFS) to automated SC injection, using the YpsoMate 2.25 and 1.0 AIs:

- Same monoclonal antibody
- Same dose and formulation
- Same injection volume
- Same injection site(s)
- An exposed needle length between 4 and 8 mm
- Slow absorption after SC injection
- Injection volume between 0.5 and 2 mL
- Similar physicochemical properties to at least one reference mAb

In regulatory submissions, it is necessary to provide a justification confirming that the specified conditions have been met.

Scientific Discussion

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 (specifically the YpsoMate 2.25 and 1.0 AIs) for monoclonal antibodies (mAbs) without additional clinical data. 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. This approach would omit the need to generate molecule-specific PK comparability assessments, as well as safety/local tolerability assessments, for new mAbs using the YpsoMate AI, provided certain conditions are met.

Table 1 Context of use and related evidence submitted at MAA

Context of Use	Proposed MIDBA evidence and reference mAbs	Additional Evidence provided for the MAA
mAbs / YpsoMate AI 1 to 1 bridge: The same total dose volume is administered with one injection both with the AI and the HHS/PFS at the same injection site.	PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab and gantenerumab. Safety and local tolerability with the YpsoMate 2.25 AI from the PK comparability studies with omalizumab and gantenerumab. Assessment of eligible mAb's PK	Safety and local tolerability from the eligible mAb's clinical development program. Subcutaneous injection sites qualified with manual injection via HHS/PFS in pivotal clinical trials for eligible mAb. Analytical comparability and formulation characterization,

	characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI device combination products in the public domain. General assessment of eligible mAb's formulation physicochemical space for MIDBA	design verification and validation, including a summative human factors study for the YpsoMate AI, being successfully completed in a population that reflects the intended use population for the eligible mAb.
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In the proposed context of use scenario, the MIDBA will be applied to eligible mAbs delivered with the YpsoMate Autoinjector (AI) containing the same formulation and injection volume of the eligible mAb formulation as that used in the pivotal clinical studies using manual injection with a PFS or HHS. The total administered dose volume should be the same for both the AI and the manual injection.

In this scenario, device and formulation properties such as plunger rod length, needle extension, exposed needle length, product formulation, osmolarity, pH, injection rate, volume and time, viscosity, needle length would need to be similar to that of the reference mAb(s).

PK comparability aspects

The CHMP *Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins* (CHMP/EWP/89249/2004) states that "The bioavailability might differ between administration sites e.g. thigh, abdomen, and relative bioavailability with respect to each administration site should be clinically investigated if alternative administration sites are to be suggested". More detailed requirements are not expressed in the guideline, though. The potential need for clinical bioavailability data for new injection devices are not described in any detail in currently available EMA guidelines.

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 would be eligible for use with the YpsoMate AI. This is endorsed.

PK comparability data previously generated for two reference mAbs with the YpsoMate AI device have been used to support the concept.

The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties similar to the ones of the reference mAb(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 parameters. Therefore, any deviation from the value of the reference mAb(s) needs to be thoroughly justified.

The Applicant proposes the MIDBA to rely mainly on data from two specific reference mAbs, i.e. mAbs for which comparative PK studies have been performed to support bridging between different devices. The two mAbs were omalizumab and gantenerumab and, for these two mAbs, PK comparability data for HHS/PFS versus YpsoMate AI have been previously generated. For these two cases, similar PK was demonstrated for SC administration via HHS/PFS and via Ypsomate AI. This would then support a similar device bridging strategy for other mAb products with similar PK and physicochemical properties, for which the other prerequisites are met (i.e. same formulation, same injected volume, etc.). While this approach appeared reasonable, the relevance of the two proposed reference mAbs (omalizumab and gantenerumab) needed further support by a discussion on the Critical Bioavailability Attributes (CBA), and Critical quality attributes (CQAs), which was lacking.

In response to the request from the SAWP to use a more quantitative approach, the Applicant created

an overview of the prerequisites for the application of MIDBA. These are presented in the following table.

Table 2 Prerequisites for the application of MIDBA to mAbs in order to achieve comparable PK between manual and automated injection

Parameter	Prerequisite	How addressed
Formulation ¹	The same for manual and automated ² administration	Control strategy
Deliverable volume	The same for manual and automated ² administration	
Monoclonal antibody ³	The same for manual and automated ² administration	
Exposed needle length ⁴	Between 4 and 8 mm for automated device	
Injection site	The same for manual and automated ² administration	Specified in medicinal product information
Absorption rate	mAbs characterized by slow absorption into systemic circulation ⁴	Selection of molecules with Tmax within "Design space"

¹Including quality and quantity of excipients.

²Autoinjector

³Including the production process and control.

⁴Supported with additional literature data for a more quantitative approach.

As stated above, to qualify for the MIDBA, the *formulation* must remain the same as that used for manual injection in the pivotal clinical studies, including overall *injection volume* and identical excipients, at the same concentrations. The same technical quality control processes will be applied to confirm the comparability of the drug product, intermediates, and development process (EMA Guideline on quality documentation for medicinal products when used with a medical device. 2021; EMA Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues. 2007; ICH Q5E Comparability of biotechnological/biological products. 2005).

The *monoclonal antibody* used for both manual and automated injection must be the same, i.e. any changes related to the cell line, production processes, or control framework compared to the mAb material studied in the pivotal clinical trials must be justified and supported with appropriate evidence according to applicable EMA guidance.

Only *injection sites* permitted for PFS or HHS injection (abdomen, upper arm, or thigh) based on clinical trial data would be eligible for use with the YpsoMate AI device. This will be specified in the product information of the mAb-device combination product.

For the *exposed needle length*, a systematic survey of biological products approved by FDA's Center for Drug Evaluation and Research (Hu et al. 2020), was referred to, including 17 biologics license applications (BLAs) with both PFS and AI presentations for SC administration. This survey revealed that most PK comparability studies met bioequivalence (BE) criteria. In addition to the injection site, the injection depth of the AI as determined by the needle length was suggested as a potential factor influencing the outcome of the PK comparability study. It was hypothesized that, in cases where BE criteria were not met, this may be attributed to AI presentations typically being administered at a 90° angle, where the extended needle length influences the effective injection depth and at a needle length >8 mm may lead to inadvertent intramuscular (IM) administrations. This differs from PFS/HHS presentations, which are generally injected at a 45° angle, without specific control over the needle length piercing the skin. Results suggest that, with a 90° insertion angle, a minimum injection depth of 4 to 5 mm is required for subcutaneous administration. A needle length of less than 8 mm would favour preventing accidental IM injection, particularly in the limbs of males and individuals with a BMI < 25 kg/m². Based on this only exposed needle length of between 4 and 8 mm for the AI platform, namely 6 mm for the YpsoMate device, can be endorsed by the CHMP.

For the parameter *absorption rate*, the Applicant suggests that monoclonal antibody therapeutics falling within the scope of using an AI platform qualified via MIDBA are generally characterized by slow absorption rates following SC injection. This reflects a slow transition from the injection site into the systemic circulation, primarily occurring via convection to the absorbing lymphatic vessels, followed by convection through the lymphatic vessels that drain into the blood (e.g., T_{max} of approximately 2 to 13 days) (Zhao et al. 2013). Thus, the underlying rationale for assuming that the PK profiles for SC administration of mAbs using HHS or PFS and AI devices will be similar is that, in such situations, the release from the interstitial space via lymph flow (Ryman and Meibohm 2017), rather than the specifics of the SC injection method, is expected to be the rate-limiting factor for absorption into the systemic circulation. This view is endorsed in principle by the CHMP. However, the design space of the MIDBA approach with respect to T_{max} and injection time has not yet been defined.

In relation to the absorption rate, the parameter *injection time* was also discussed in relation to local tolerability at the injection site (see below). From a PK perspective, in view of the slow absorption of mAbs after SC injection as discussed above, a difference in seconds when it comes to injection time is hardly expected to affect PK parameters. The Applicant has confirmed that for the YpsoMate AI, the specification demands the solution to be administered within 15 seconds or less. 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. Hence, from a PK point of view, the slight differences in injection time between manual and automated injection are not deemed relevant for a SC injected mAb. However, as already stated, thresholds for clinically relevant differences are not established.

Support from an expanded validation set

To further support the MIDBA concept from a quantitative perspective, the Applicant expanded their previous overview of PK comparability studies with additional studies for in-house and external mAbs. This validation set comprised three subsets:

- Validation set 1, including studies with mAbs that are commercially available from other manufacturers with the YpsoMate AI platform, 1.0 and 2.25 mL (n=11). However, PK comparability data were not available to the Applicant.
- Validation set 2 including studies with mAbs from the Applicant's pipeline (n=4)
- Validation set 3 combining validation sets 1 and 2 and including additional studies with

additional mAbs outside of the Applicant's portfolio (n=34).

Based on the described validation sets, the Applicant concluded that PK comparability could be established without a clinically relevant impairment of the local tolerability for the concerned mAbs. Time to reach maximum serum concentration (T_{max}) was selected as the most relevant PK parameter for eligibility of a mAb for the application of the MIDBA.

In the comparison of SC administration of the same mAb formulation via PFS or AI, one potential source of absorption differences may be related to SC fluid depot. Differences in shape of the fluid depot could result in differences in drug transport from such depot to the lymphatic vasculature and, thus, in different residence times in the SC tissue. Impact of residence time differences between PFS and AI would be reflected on differences in T_{max} values.

For the mAbs in the validation set, comparable average and ranges of T_{max} values were described for automated and manual injection. This supports similar absorption rates for AI and PFS.

There was a wide range of individual T_{max} values, however, suggesting marked inter-subject variability in the absorption process. The precise root cause of the marked inter-subject variability is unknown and may include physiology differences at the SC administration site. It is expected that such inter-individual variability is more pronounced compared to any potential differences from the different injection procedures within the MIDBA concept. This conclusion is supported by the observation that in the evaluated PK comparability studies, the median T_{max} values from PFS/HHS and AI were identical or very similar despite the high ranges of individual T_{max} values for both administration methods.

For parameters related to *mAb formulation physicochemical and device characteristics*, the Applicant described the physicochemical parameters of mAb formulations from their portfolio (i.e. validation set 2). In the BE studies comparing manual versus automated administration, various AI and OBDS devices were used. The Active Pharmaceutical Ingredient (API) concentration in the SC formulations ranged between 120 and 180 mg/mL. The pH of the dosing solutions varied from 5.5 to 6, osmolality from 259 to 372 mOsm/Kg, and viscosity from 4.6 to 8.7 cP. The isoelectric point (pI) of the molecules ranged from 8.98 to 9.5. Due to the relatively small number of mAbs, the Applicant acknowledged that this validation set remains descriptive and is considered too small to form a comprehensive framework. This view is endorsed, and it can be concluded that based on these data, no specific physicochemical and/or device characteristics have been possible to identify as critical parameters for acceptance of the MIDBA concept.

Overall, when it comes to parameters to define a certain "design space" for applicability of the MIDBA as an alternative to conducting a comparative PK study, the Applicant has compiled data from several studies comparing PFS/HHS and an AI, in addition to the data obtained for omalizumab and gantenerumab, regarded as reference mAbs.

While the approach may still be regarded as mainly descriptive, certain boundaries have been defined, such as the exposed needle length, which is proposed to be in the range 4-8 mm (to obtain an injection depth for an AI that is similar to that with a manual injection via PFS/HHS and avoid IM injection) and a slow absorption. For the latter, a specified T_{max} range has not been proposed, other than that T_{max} should be "in a range of days". A median T_{max} in the range of 3-8 days was observed both for manual and automated injection in the presented validation dataset.

No specific physicochemical characteristics have been identified and put forward as critical parameters for acceptance of the MIDBA concept, acknowledging, however, that mainly descriptive data have been provided for those parameters. This can be accepted for the proposed CoU, covering only monoclonal antibodies with similar physicochemical properties as at least one reference product and with slow absorption.

192 Safety and local tolerability aspects

193 Introducing an AI platform under the conditions described above as an alternative to manual injection
194 via PFS or HHS is not expected to impact the systemic safety profile of the mAb, as long as PK
195 comparability/equivalence can be assumed.

196 Data on the local tolerability profile of a mAb following manual SC administration using PFS or HHS will
197 always be available from previous clinical trials and should encompass injection volumes that cover the
198 range of injection volumes foreseen to be delivered with the YpsoMate AI platform. The formulation
199 must be the same. Thus, with similar depth and speed of injection for AI vs. PFS/HHS, this should
200 result in minimum differences in local tolerability, as long as the formulation, injected volume and
201 injection site(s) remain the same. The angle and depth of injection is, in principle, expected to be more
202 variable with manual injections compared with injections using an AI device.

203 The Applicant provided comparative data on tolerability between manual and automated injections
204 from bioequivalence (BE) studies involving the reference monoclonal antibodies omalizumab and
205 gantenerumab. Additionally, they shared findings from user preference, usability, and satisfaction
206 studies conducted with mAbs from Validation sets 2 and 3, which compared manual injection methods
207 with autoinjector or pen devices.

208 The CHMP agrees that in the context described above clinically relevant differences in the local
209 tolerability between AI and manual injection are not expected. However, due to the inherent
210 challenges in defining the drivers of local tolerability, the omission of dedicated local tolerability
211 assessments based on MIDBA should be supported by a separate, case-specific, justification.

212 Analytical comparability and formulation characterization, design verification, validation, and
213 summative human factors study

214 In future marketing authorisation applications with an YpsoMate AI drug delivery device, a complete
215 design verification and validation technical package will be included. In addition, a summative human
216 factors study in a population that reflects the intended use population for the eligible mAb will be
217 submitted.

218 This approach is endorsed and assumes that analytical comparability and formulation characterization,
219 design verification and validation, including the human factors study, for the YpsoMate AI will be
220 successfully conducted for the eligible mAb.

221 Alignment with the requirements in the CHMP *Guideline on quality documentation for medicinal*
222 *products when used with a medical device* (EMA/CHMP/QWP/BWP/259165/2019) is expected, unless
223 thoroughly justified.

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225 **Annexes to be published:** (redacted for COU2-5 and commercially confidential information)

- 226 1. Briefing document
- 227 2. List of issues
- 228 3. Written responses to list of issues
- 229 4. Discussion meeting presentation