Molecule Independent Device Bridging Approach (MIDBA) Qualification of Novel Methodology Procedure EMA/SA/0000176027

EMA Discussion Meeting with Applicant

9 April 2025 |

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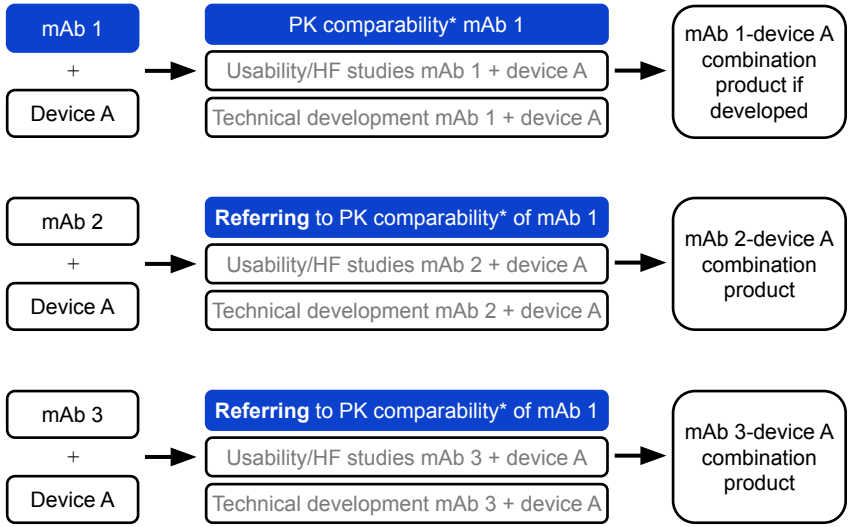
MIDBA Novel Methodology for Medicine Development

Molecule Independent Device Bridging Approach (MIDBA)

- Pivotal trials often conducted without final delivery device
- Alternative methodology to the conduct of dedicated comparative PK studies for demonstration of equivalence of manual vs automated SC injection administration methods
- Bridging between clinical (HHS or PFS) & commercial (AI [redacted] platform) drug delivery device presentations for registration leveraging previously generated BE data with reference mAbs and same device platform
- Technical Design Verification & Validation, including a summative human factors study to be conducted for each medicinal product individually



Following multiple medicinal product programs CHMP SAs, recommendation to submit a Qualification Procedure for MIDBA
Novel methodology to support registration of Roche mAbs with YpsoMate AI platform [redacted]

HHS: handheld syringe ; PFS: prefilled syringe; mAb: monoclonal antibody ; BE: bioequivalence; AI: autoinjector; [redacted] SA: Scientific Advice

MIDBA Qualification's Contexts of Use (CoUs)

- Roche mAb medicinal products with Ypsomate Auto-Injector (AI) platform (YpsoMate 2.25 & 1.0)
  - **CoU1:** "1:1 bridging" same injection volume between manual and automated injection

[redacted]

MIDBA Qualification List of Issues for Discussion

Overarching question applicable to all CoUs - Question 1

Please discuss the need for a more quantitative approach to establish the appropriateness of the clinical validation set, as well as the criteria for assessment of the eligibility of mAbs based on PK characteristics, mAb formulation physicochemical and device characteristics spaces. This is currently lacking throughout all the proposed CoUs.

Structure for the Applicant's Answer to Question 1:

1. A discussion of the need for a more quantitative approach to establish the appropriateness of the clinical validation set.
2. A systematic review of PK and local tolerability results from various PK comparability studies with mAbs to extend the clinical validation set.
3. Criteria for assessing mAb eligibility based on PK characteristics, physicochemical properties of mAb formulations, and device characteristics ("design space").

Conceptual discussion covering any device type [redacted]

Overarching question applicable to all CoUs - Question 1

1. A discussion of the need for a more quantitative approach to establish the appropriateness of the clinical validation set: <u>Achieving PK comparability between manual and automated injection</u>

Prerequisites for MIDBA application to mAbs to achieve comparable PK between manual & 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 product label
Absorption rate	mAbs characterized by slow absorption into systemic circulation[4]	Selection of molecules with Tmax within “Design space”

[1]Including quality and quantity of excipients; [2]Autoinjector or OBDS; [3]Including the production process and control; [4]Supported with additional literature data.

Overarching question applicable to all CoUs - Question 1

1. A discussion of the need for a more quantitative approach to establish the appropriateness of the clinical validation set: Achieving an acceptable local tolerability profile with manual & automated injection

Prerequisites for MIDBA application to mAbs to achieve a comparable local tolerability profile between manual & automated injection.

Parameter	Prerequisite	How addressed
Underlying disease	The same for manual and automated[2] administration	Specified in product label
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	
Injection site	The same for manual and automated[2] administration	Specified in product label
Injection methodology (incl. Injection force/time, needle length and gauge)[4]	Local tolerability studied in pivotal clinical studies in the target population following manual injection Manual versus automated injection data from local tolerability study from the first molecule utilizing the platform (either PK comparability study in healthy subjects or clinical study in target population) Needle length between 4 and 8 mm for automated device	Control strategy
Professional supervision[4]	Proper training of self-administration	Training materials

[1]Including quality and quantity of excipients; [2]Autoinjector or OBDS; [3]Including the production process and control; [4]Supported with additional literature data.

Overarching question applicable to all CoUs - Question 1

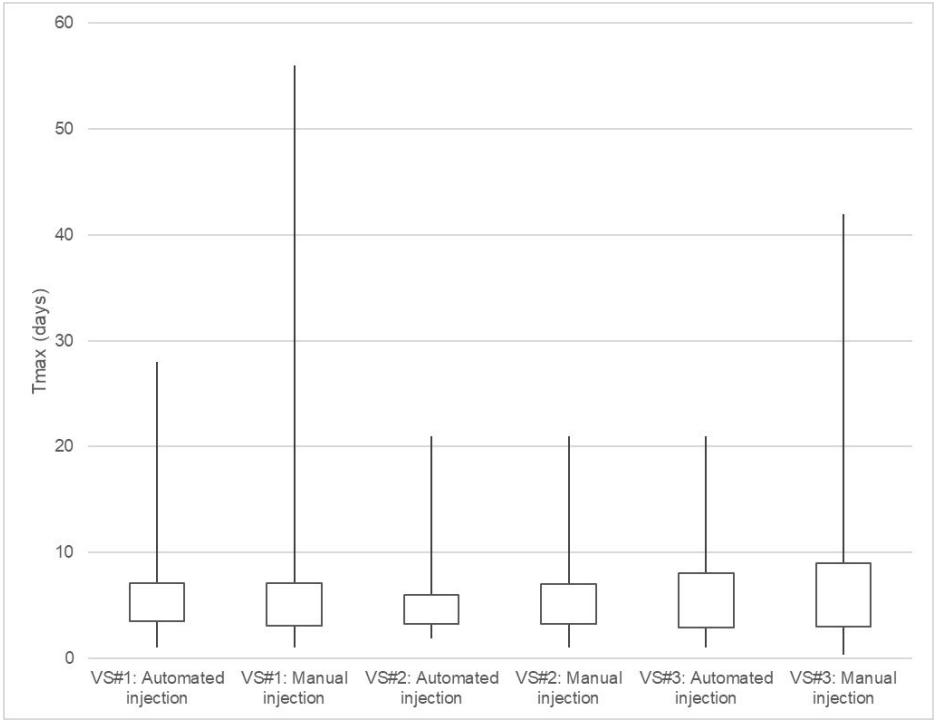
2. A systematic review of PK and local tolerability results from various PK comparability studies with mAbs to extend the clinical validation set.

Clinical validations sets based on PK comparability studies between manual & automated subcutaneous mAb administration

Validation sets	Data sources (PK comparability studies)	No. mAbs	Relevant information
1	mAbs approved with YpsoMate AI	11	- Comparative Tmax - Comparative local tolerability - Molecule type / weight - Injection volume - Formulation ingredients - mAb concentration Figures in back up
2	mAbs in the Applicant's portfolio	4	
3	Combined validation set: 1 and 2 plus additional mAbs outside of the Applicant's portfolio	34	

- Methodologies for local tolerability assessments differ across PK comparability studies and typically do not specify device types, needle length or needle gauge, nor differences in injection speed manual vs automated administration.
- Majority of studies (but not all of them) powered to statistically demonstrate BE.
- Due to these methodological differences, the Applicant applied a predominantly descriptive approach when comparing local tolerability findings from these trials.

3. Criteria for assessing mAb eligibility based on PK characteristics, physicochemical properties of mAb formulations, and device characteristics (“design space”)



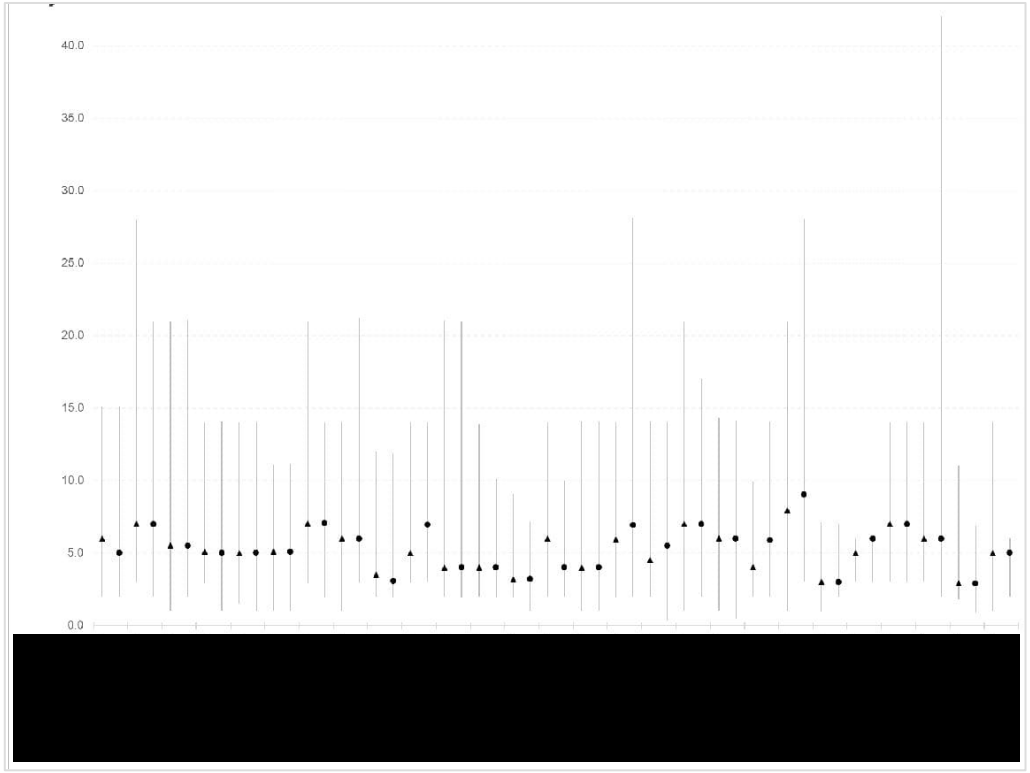
The lower and upper horizontal lines of the boxes indicate the range of the medians and the vertical lines represent the minimum and maximum range around the median.
VS: validation set.

Rationale for selecting Tmax as most relevant PK parameter for MIDBA

- Comparison of SC absorption from PFS and AI needs consideration of SC absorption process and depot shape.
- Direct blood capillary absorption is likely precluded due to mAbs size.
- mAbs move through SC tissue via convection or diffusion to lymphatic vasculature.
- Slow release into lymphatic system results in Tmax of ~2–8 days for SC-administered mAbs.
- Depot shape differences between PFS and AI with a clinically relevant impact on drug transport would be reflected in Tmax values.

Overarching question applicable to all CoUs - Question 1

3. Criteria for assessing mAb eligibility based on PK characteristics, physicochemical properties of mAb formulations, and device characteristics (“design space”)



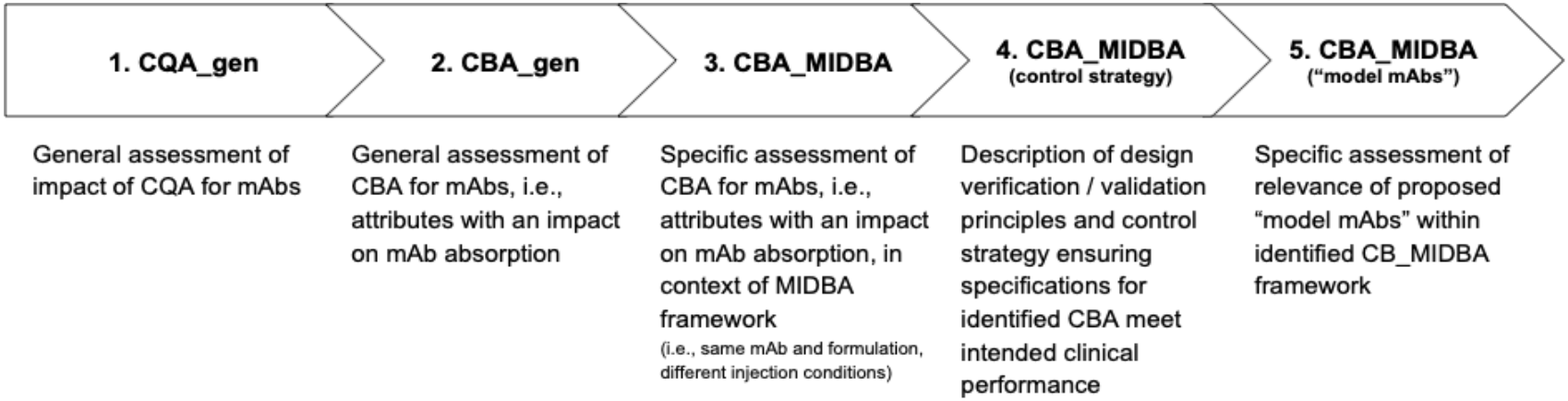
▲ Tmax median - Automated injection; ● Tmax median - Manual injection; — Tmax limit ranges

- Comparable Tmax values for automated and manual injection of the same mAb.
- Very similar observed Tmax ranges, indicating similar absorption from AI and PFS.
- Wide range of individual Tmax values suggests significant inter-subject variability in absorption.
- Variability root cause may include physiological differences at the SC administration site.
- Inter-individual variability likely more pronounced than differences from injection procedures.
- Meta-analysis supports comparable absorption and systemic exposure from AI & PFS injections.

Other questions under “Scientific discussion”

The relevance of the two proposed “model mAbs” (omalizumab & gantenerumab) should be supported by a discussion on the Critical Bioavailability Attributes (CBA), and Critical quality attributes (CQAs), which is currently lacking.

Stepwise assessment of CQA & CBA relevant for the MIDBA approach



- **Identified CBA-MIDBA: exposed needle length and deliverable volume.**
- **Rigorous control strategy** based on regulatory guidelines to meet intended clinical performance, incl. Design Verification Testing, Testing at Release, Testing during Stability at Process Performance Qualification (PPQ).

[redacted]

CoU1 [mAb YpsoMate AI “1:1”] - Question 2

The Applicant proposes to limit the application of MIDBA to products with PK characteristics and formulation properties within the studied design space where in vivo data is available (isotype, injection volume, concentration, injection time, formulation ingredients, bioavailability values, Tmax values).

In line with the general question above, the Applicant has however not defined which actual limits for these parameters they have in mind and is therefore invited to present the proposed “design space” more explicitly, including a justification of the relevance of the proposed reference drugs for CoU1.

Refer to overarching question applicable to all CoUs.

CoU1 [mAb YpsoMate AI “1:1”] - Question 3

Using the MIDBA, no clinical safety or tolerability data would be available for the device bridged to (e.g. from PFS/HHS to AI). In the BE studies with the reference mAbs omalizumab and gantenerumab, the rates of ISRs were somewhat higher for the AI vs. PFS/HHS (24% vs. 14% for omalizumab and 40.7% vs. 27.5% for gantenerumab). The issue is therefore not only the injection volume but the amount/time (rate) that might be higher with the AI and have an impact on the safety and tolerability. This should be discussed.

- Gantenerumab BE study
  - Dosing was within 10 seconds (HHS) and under 15 seconds (AI): Unlikely to have affected ISRs.
  - Differences may be due to the higher AI fill volume (1.77 mL) versus HHS (1.70 mL) from methionine addition.
  - Despite formulation differences, BE was achieved, indicating gantenerumab remains a relevant "model mAb." Slow SC tissue absorption, rather than injection method, is the main factor for Tmax.
  - All but one ISRs (injection site discoloration) were of mild intensity and resolved without sequelae.

- Omalizumab BE study
  - No injection instructions found.
  - The higher ISR rate for AI versus PFS may be due to faster injection or stronger skin pressure.
  - All ISRs were of mild intensity and resolved without sequelae.

[redacted]

In conclusion, **for the volumes delivered with AI platforms of up to 2 mL**, differences in the actual injection speed following more variable manual vs. more standardized automated injection are not expected to result in clinically relevant differences in the local tolerability profile of the mAb.

CoU1 [mAb YpsoMate AI “1:1”] - Question 4

There seem to be no robust data supporting that injection times for the YpsoMate AI remain consistent and within the injection time range of the vial syringe or prefilled syringe. This should also be discussed.

- Control strategy, based on regulatory guidelines, ensures YpsoMate AI administers the solution within 15 seconds or less.
- Injection times in pivotal clinical studies vary based on HCP preferences and capabilities, while the AI platform standardizes this rate to be within the manual injection range.
- In Ph3 studies, injection time is typically not recorded for manual injections and HCPs follow established guidelines for SC administration of volumes under 2 mL, which include selecting the injection angle and site, but not the injection rate.

Brevacta study (tocilizumab) CSR - Results for PFS Observer
Question 8: *How long did it take to inject the medication (seconds)?*

User type	Min	Mean	Max	Standard deviation	Total users
Patient	5	15.8	30	5.8	28
Non-professional caregiver	3	9.3	15	6.0	3
Professional caregiver	15	40.3	80	21.2	8
Overall results	***3***	***20.3***	***80***	***14.7***	***39***

- Dedicated studies did not reveal a general impact of injection time on local tolerability and pain sensation.
- Confounding factors, such as dosing solution composition or injection site, complicate definitive conclusions.
- Finding particularly relevant for MIDBA, as the formulation and active molecule remain the same regardless of the injection method.

HCP: healthcare provider

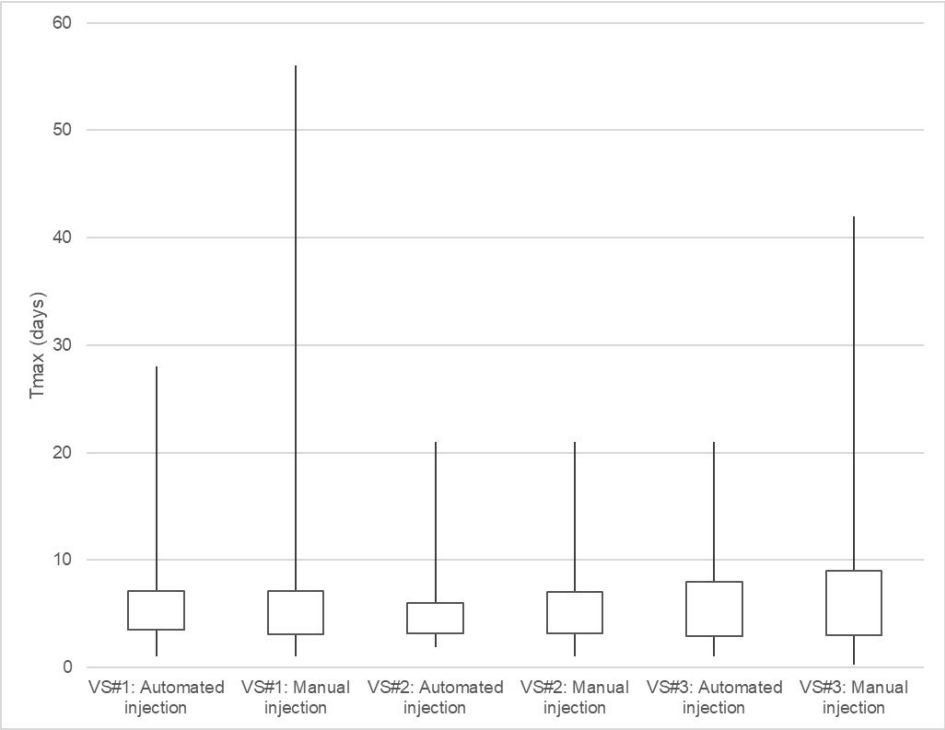
Revised CoU1 Scenario and the Proposed Supporting Evidence Available with the MAA

Context of Use	Proposed MIDBA evidence and reference mAbs	Additional Evidence provided for the MAA
Scenario 1 / CoU1 **mAbs / YpsoMate AI 1 to 1 bridge[a]:** The same total dose volume is administered with one injection both with the AI and the HHS/PFS at the same injection site. **Injection volumes up to 2 mL.**	PK comparability data (i.e., HHS/PFS versus YpsoMate AI) previously generated for omalizumab[c], gantenerumab, [redacted] **and for other mAb-AI combination products in the public domain.** Safety and local tolerability with the YpsoMate 2.25 AI from the PK comparability studies with omalizumab[c] and gantenerumab **and from other mAb-AI combination products in the public domain.** Assessment of eligible mAb's PK and local tolerability characteristics space based on proposed reference mAbs and mAb-YpsoMate 1.0 mL and 2.25 mL AI **and other mAb-AI** combination products in the public domain. General assessment of eligible mAb's formulation physicochemical space for MIDBA.	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, 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.

Prerequisites: The integral drug-YpsoMate AI device combination product contains the same formulation (i.e., including the same excipients at the same concentrations) and injection volume as that injected manually in the pivotal clinical studies (using a HHS/PFS).

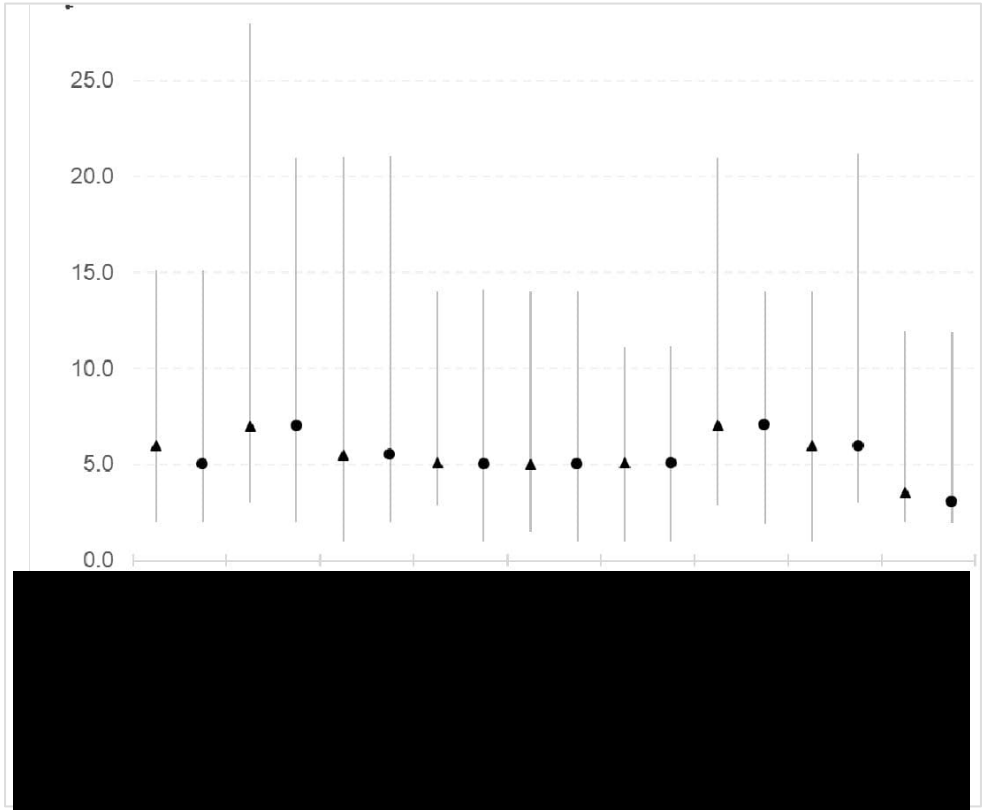
Backup slides

Figure 1. Clinical validation sets based on PK comparability studies between manual and automated SC administration - Tmax median and limit ranges per validation set and injection methodology.



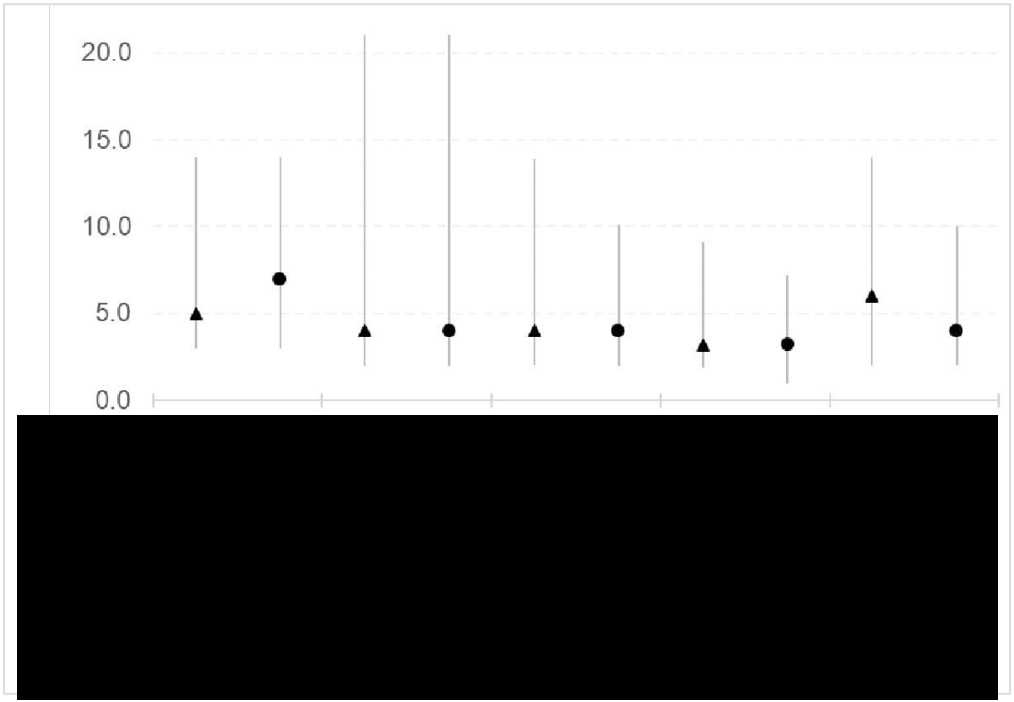
The lower and upper horizontal lines of the boxes indicate the range of the medians, and the vertical lines represent the minimum and maximum range around the median.
VS: validation set.

Figure 2a. Tmax median values and ranges for each study, validation set 1 (mAbs approved with YpsoMate AI).



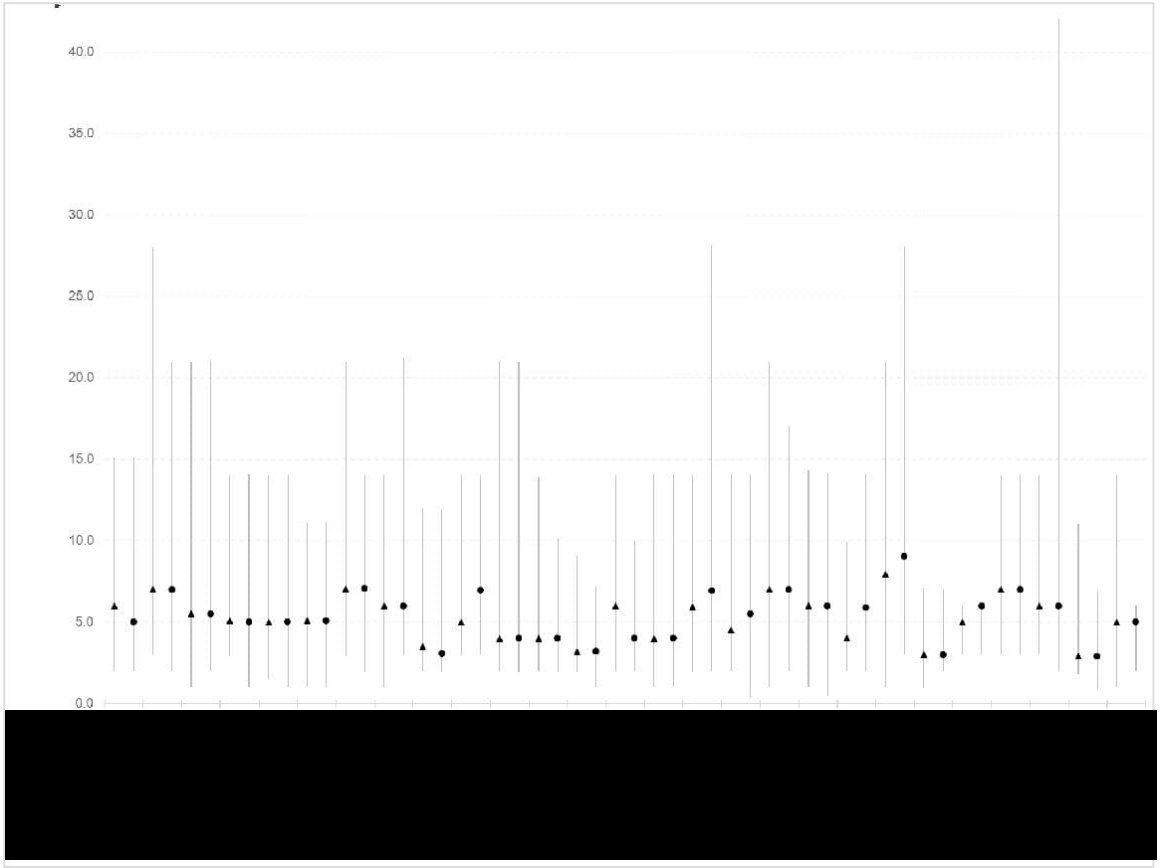
▲ Tmax median - Automated injection; ● Tmax median - Manual injection; — Tmax limit ranges

Figure 2b. Tmax median values and ranges for each study, validation set 2 (mAbs from the Applicant's pipeline).



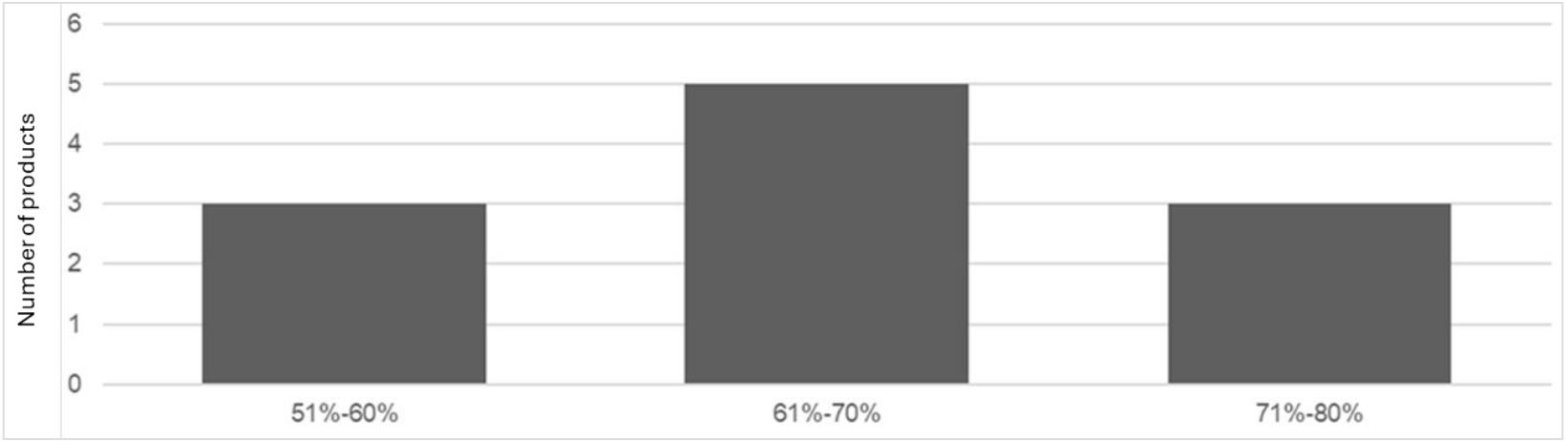
▲ Tmax median - Automated injection; ● Tmax median - Manual injection; — Tmax limit ranges

Figure 2c. Tmax median values and ranges for each study, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2).



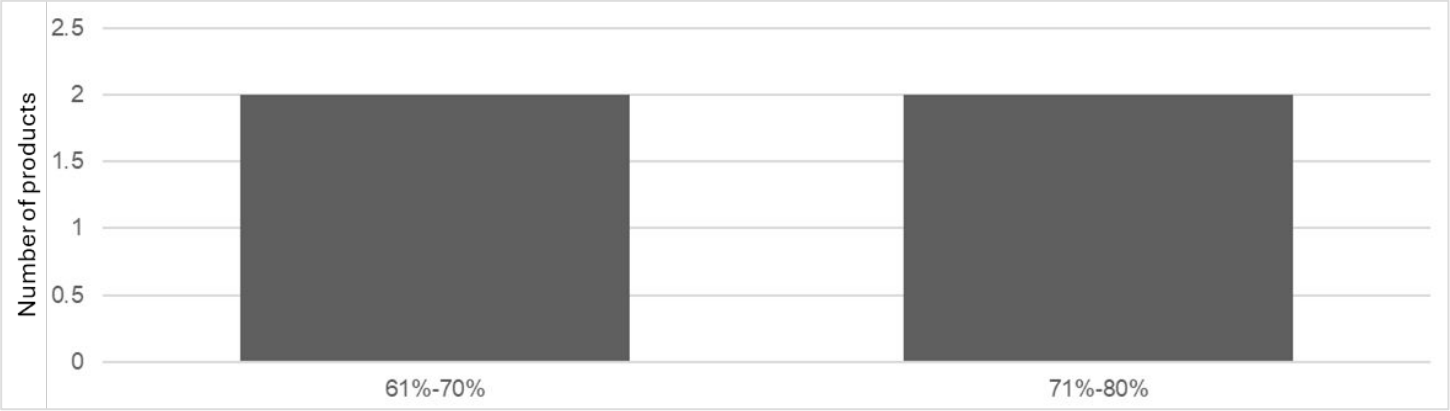
▲ Tmax median - Automated injection; ◘ Tmax median - Manual injection; — Tmax limit ranges

Figure 3a. Bioavailability, validation set 1 (mAbs approved with YpsoMate AI).



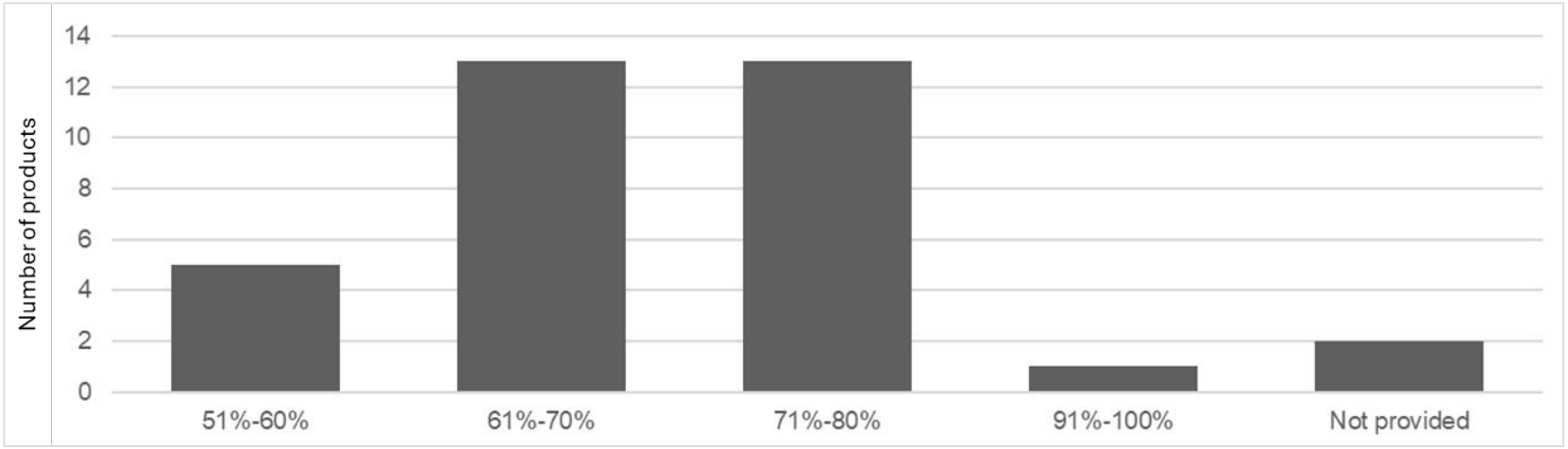
Bars indicate the number of mAbs categorized within bioavailability ranges of 51%-60%, 61%-70%, and 71%-80%.

Figure 3b. Bioavailability, validation set 2 (mAbs from the Applicant's pipeline).



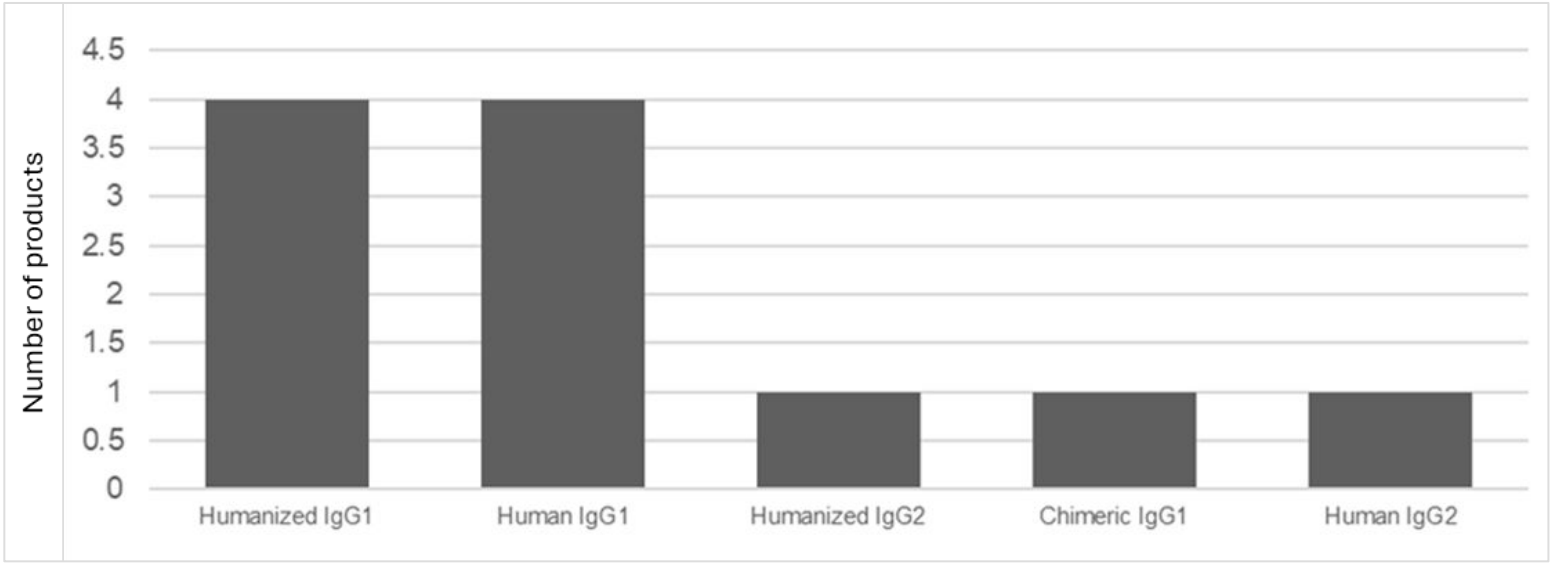
Bars indicate the number of mAbs categorized within bioavailability ranges of 61%-70% and 71%-80%.

Figure 3c. Bioavailability, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2).



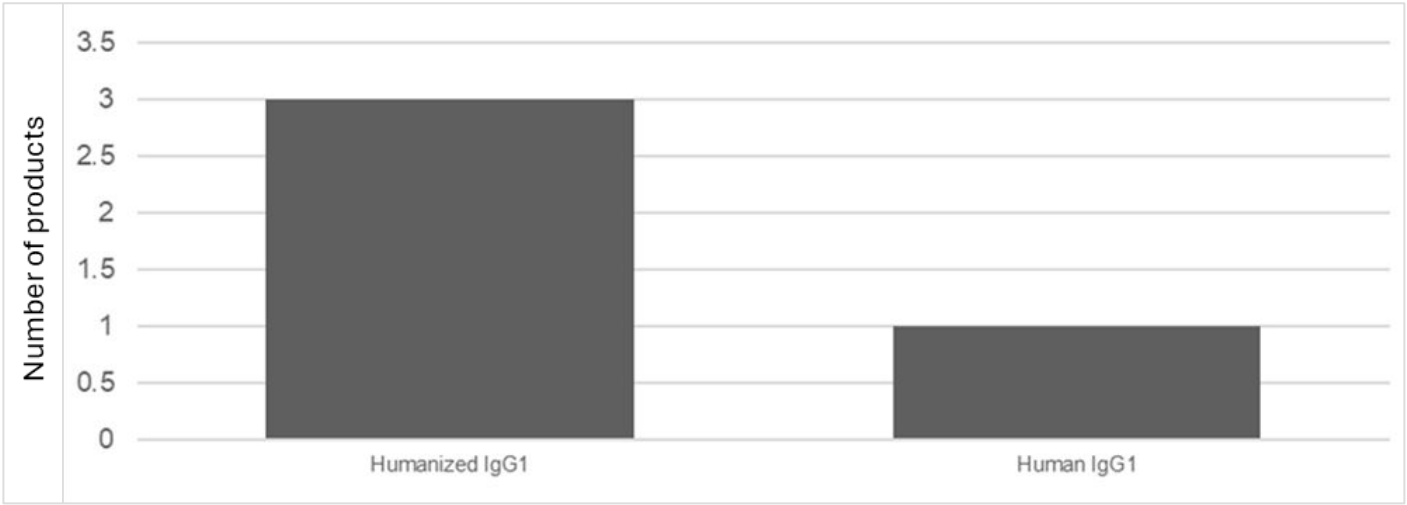
Bars indicate the number of mAbs categorized within bioavailability ranges of 51%-60%, 61%-70%, 71%-80%, 91%-100%, and not available.

Figure 4a. Molecule type, validation set 1 (mAbs approved with YpsoMate AI).



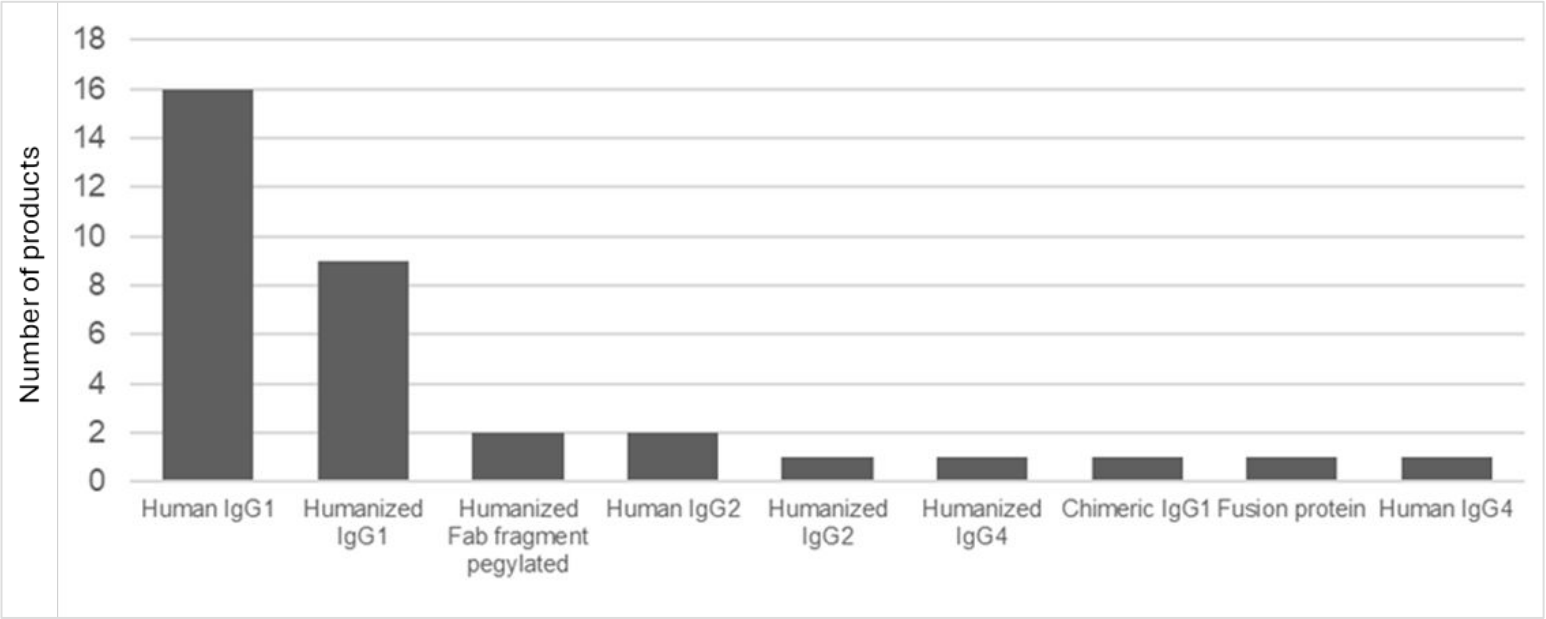
Bars indicate the number of molecules within the different mAb types.

Figure 4b. Molecule type, validation set 2 (mAbs from the Applicant's pipeline).



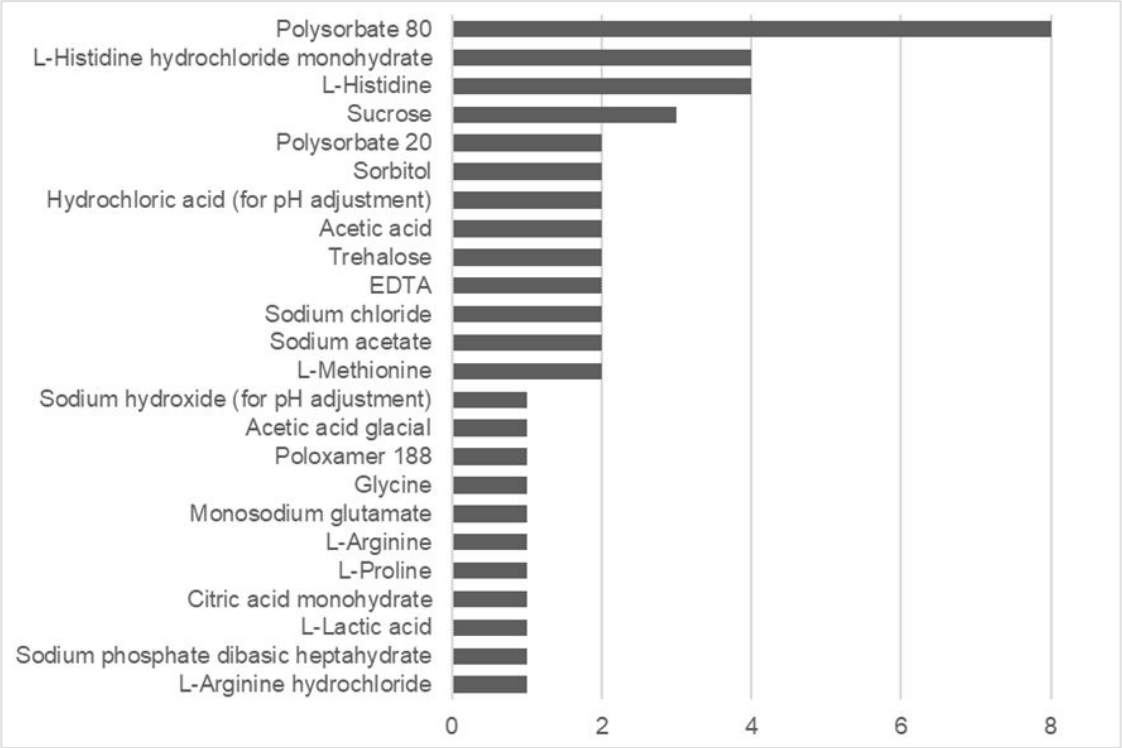
Bars indicate the number of molecules within the different mAb types.

Figure 4c. Molecule type, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2).



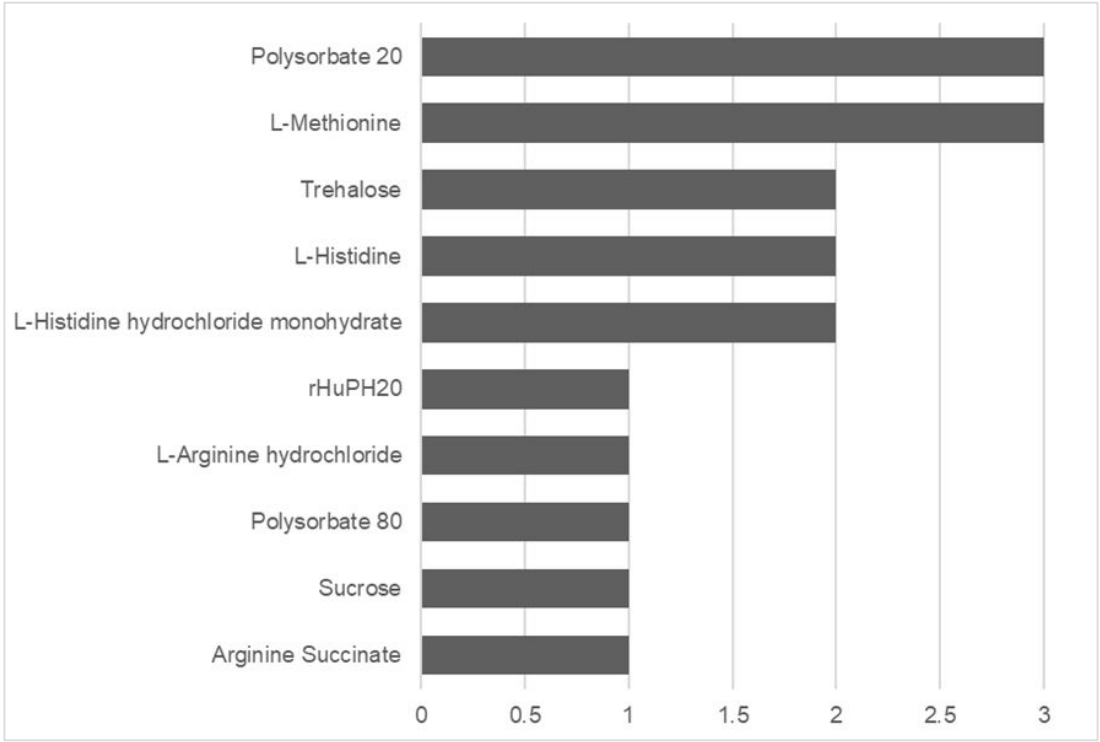
Bars indicate the number of molecules within the different molecule types.

Figure 5a. Formulation excipients, validation set 1 (mAbs approved with YpsoMate AI).



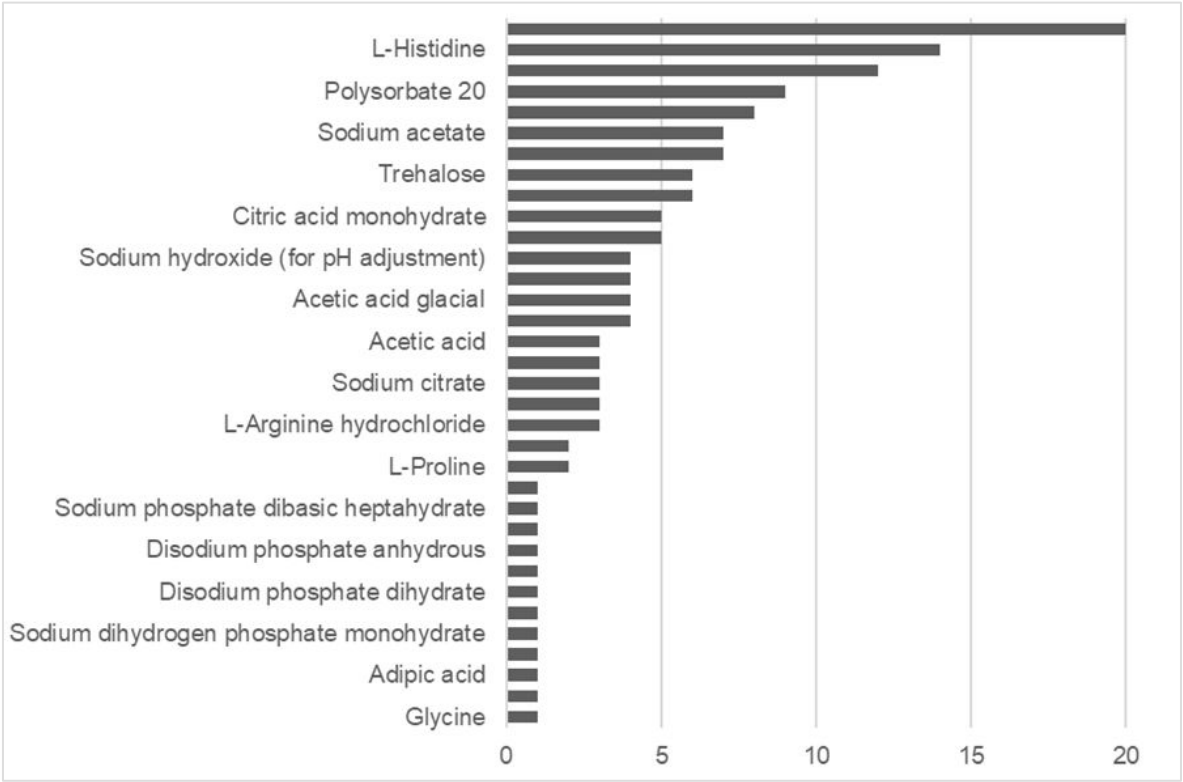
Bars indicate the number of molecules within the different mAb types.

Figure 5b. Formulation excipients, validation set 2 (mAbs from the Applicant's pipeline).



Bars indicate the number of molecules within the different mAb types.

Figure 5c. Formulation excipients, validation set 3 (mAbs from other manufacturers combined with validation sets 1 and 2).



Bars indicate the number of molecules within the different molecule types.

MIDBA EU Qualification – BP questions

The Sponsor intends to apply the MIDBA as an alternative methodology to conducting dedicated clinical PK comparability studies between manual and automated subcutaneous injection drug delivery device platforms for eligible monoclonal antibodies [redacted].

The Sponsor proposes applying the novel MIDBA methodology across a number of different context of use (CoU) scenarios, each supported by a distinct scientific evidence base. This approach should enable a tailored discussion on the regulatory qualification of this novel methodology for each CoU.

Q1: In CoU scenario 1, the integral mAb drug-YpsoMate 1.0 mL and 2.25 mL AI device combination product presentation to be submitted with the marketing authorisation application (MAA) contains the same injection volume of a mAb formulation as that used in the pivotal clinical studies (manual injection using a PFS or HHS). The total dose volume is administered with one injection both with the AI and the PFS or HHS.

Does the Agency agree that for this CoU, the MIDBA can be applied for clinical qualification of the YpsoMate AI platform, so that eligible mAbs can refer to available PK comparability data previously generated with reference mAbs?