Physiologically Based Predictions of Monoclonal Antibody Pharmacokinetics: Insights from a Large-Scale Data Analysis

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3. Computational Pharmacology and Clinical Oncology (COMPO) Team, Inserm UMR1068, CNRS UMR7258, Aix Marseille University, France

Physiologically Based Predictions of Monoclonal Antibody Pharmacokinetics: Insights from a Large-Scale Data Analysis

- A large database of pharmacokinetic data for mAbs compiled from the literature
- Support early-stage pharmacokinetic predictions of mAbs and FIH trials
- Naïve model-based predictions of clinical PK after IV and SC administration

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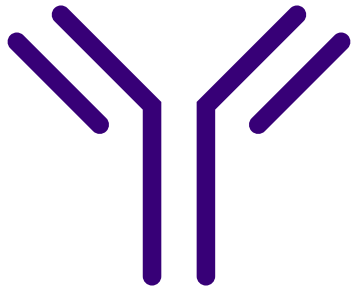
Monoclonal antibodies and subcutaneous administration

Therapeutic monoclonal antibodies (mAbs)



1. Crescioli S, Kaplon H, Chenoweth A, et al Antibodies to watch in 2023
2. K. P. Martin et al Trends in industrialization of biotherapeutics: a survey of product characteristics of 89 antibody-based biotherapeutics .Mabs. vol. 15. no. 1. 2023

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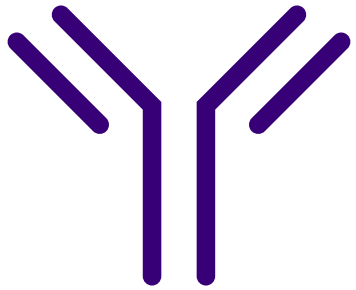
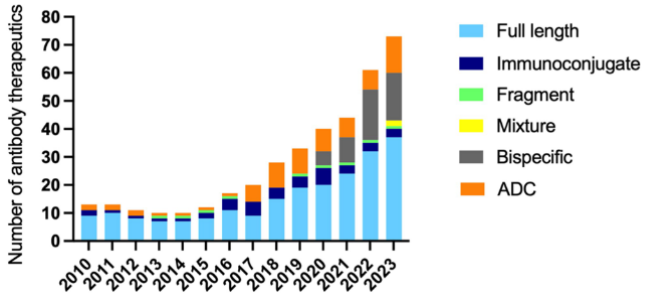
The number of approved mAbs has been growing significantly in recent years[1]





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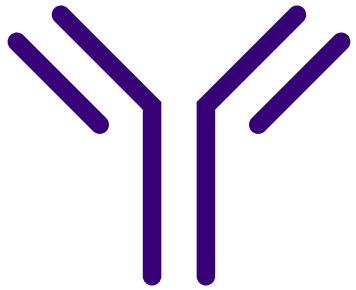
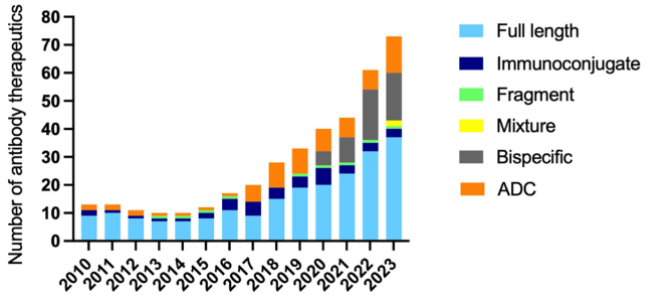
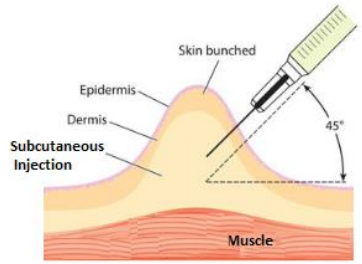
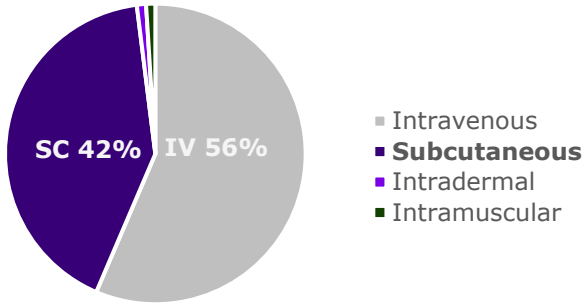
Almost half of the marketed antibodies are administered subcutaneously[2]









Despite longstanding use, many aspects of the bioavailability remain poorly understood

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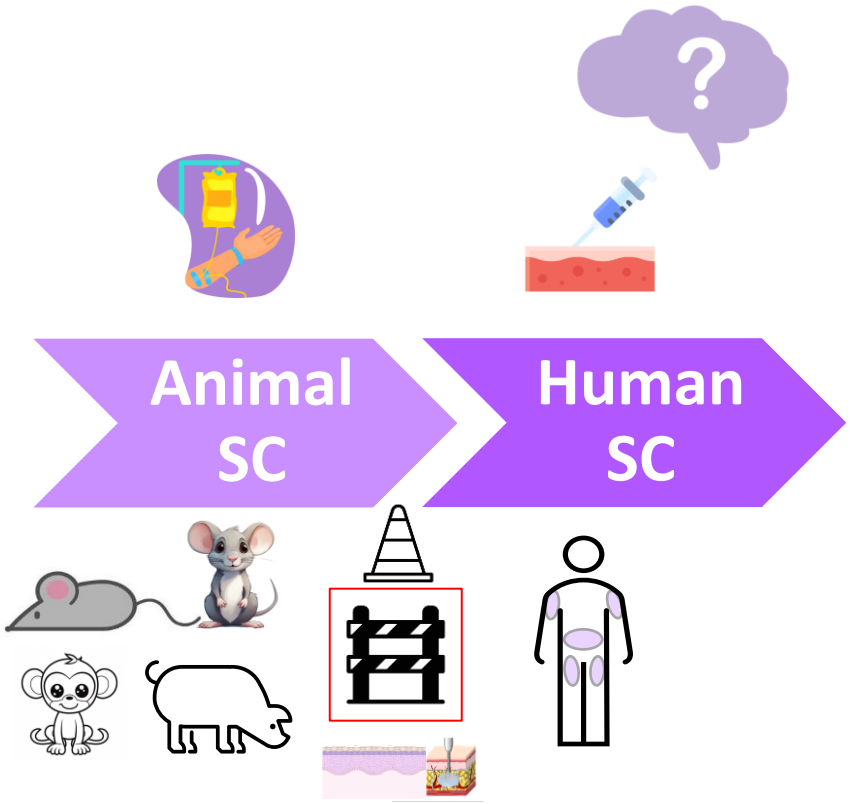
Prediction of monoclonal antibodies pharmacokinetics after subcutaneous administration



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3. https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement monoclonal-antibodies-and-other-drugs

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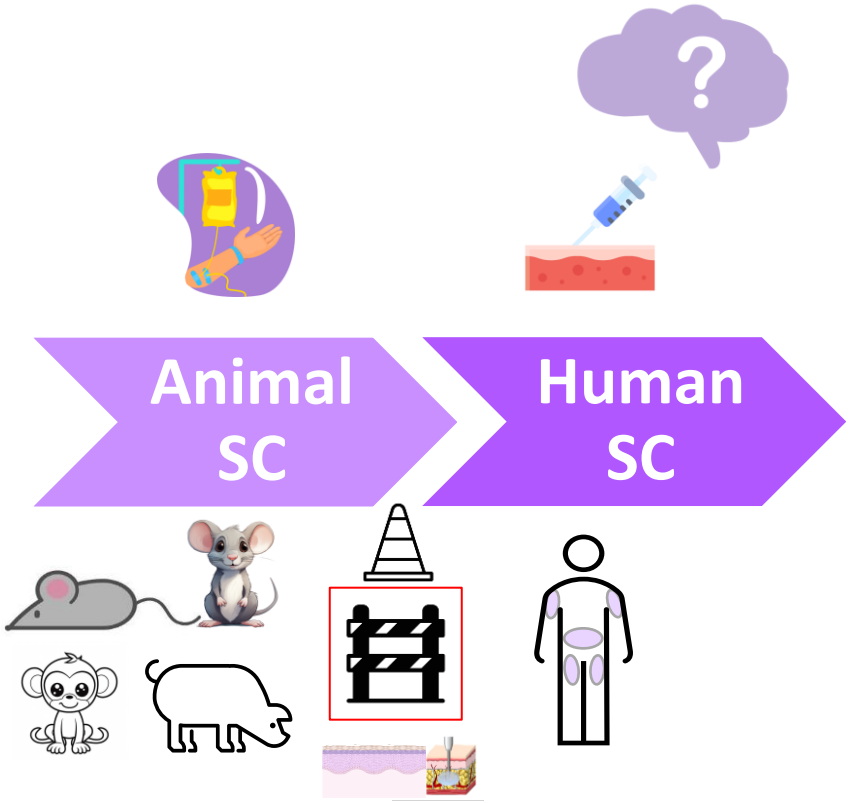

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

For Immediate Release: April 10, 2025

Today, the U.S. Food and Drug Administration is taking a groundbreaking step to advance public health by replacing animal testing in the development of monoclonal antibody therapies and other drugs with more effective, human-relevant methods. The new approach is designed to improve drug safety and accelerate the evaluation process, while reducing animal experimentation, lowering research and development (R&D) costs, and ultimately, drug prices.

The FDA's animal testing requirement will be reduced, refined, or potentially replaced using a range of approaches, including AI-based computational models of toxicity and cell lines and organoid toxicity testing in a laboratory setting (so-called New Approach Methodologies or NAMs data). Implementation of the regimen will begin immediately for investigational new drug (IND) applications, where inclusion of NAMs data is encouraged, and is outlined in a roadmap also being released today. To make determinations of efficacy, the agency will also begin use pre-existing, real-world safety data from other countries, with comparable regulatory standards, where the drug has already been studied in humans.

"For too long, drug manufacturers have performed additional animal testing of drugs that have data in broad human use internationally. This initiative marks a paradigm shift in drug evaluation and holds promise to accelerate cures and meaningful treatments for Americans while reducing animal use," said FDA Commissioner Martin A. Makary, M.D., M.P.H. "By leveraging AI-based computational modeling, human organ model-based lab testing, and real-world human data, we can get safer treatments to patients faster and more reliably, while also reducing R&D costs and drug prices. It is a win-win for public health and ethics."

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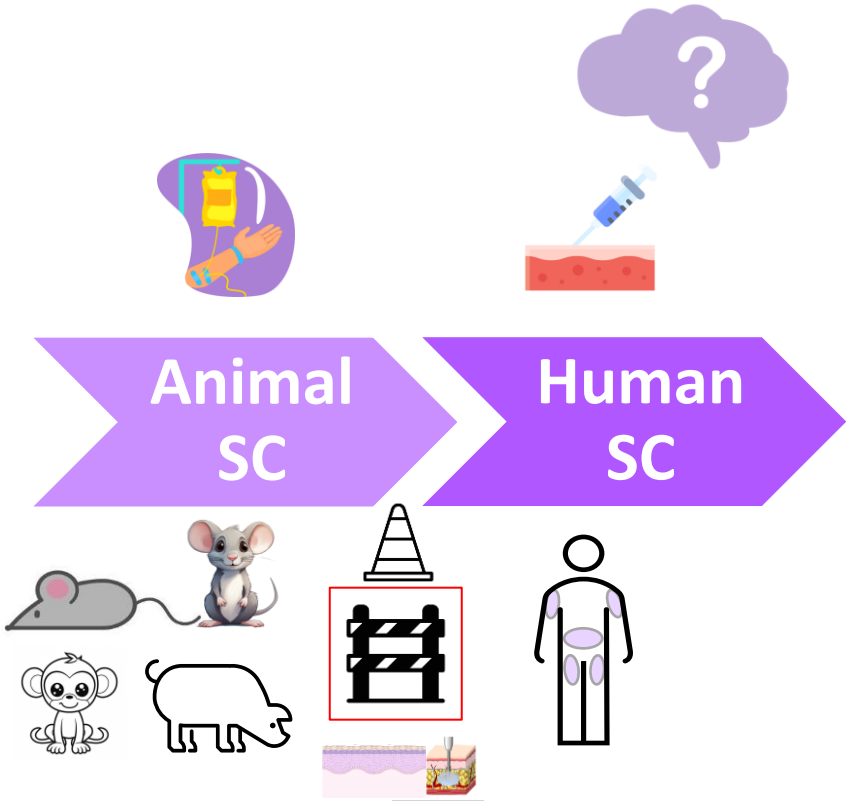

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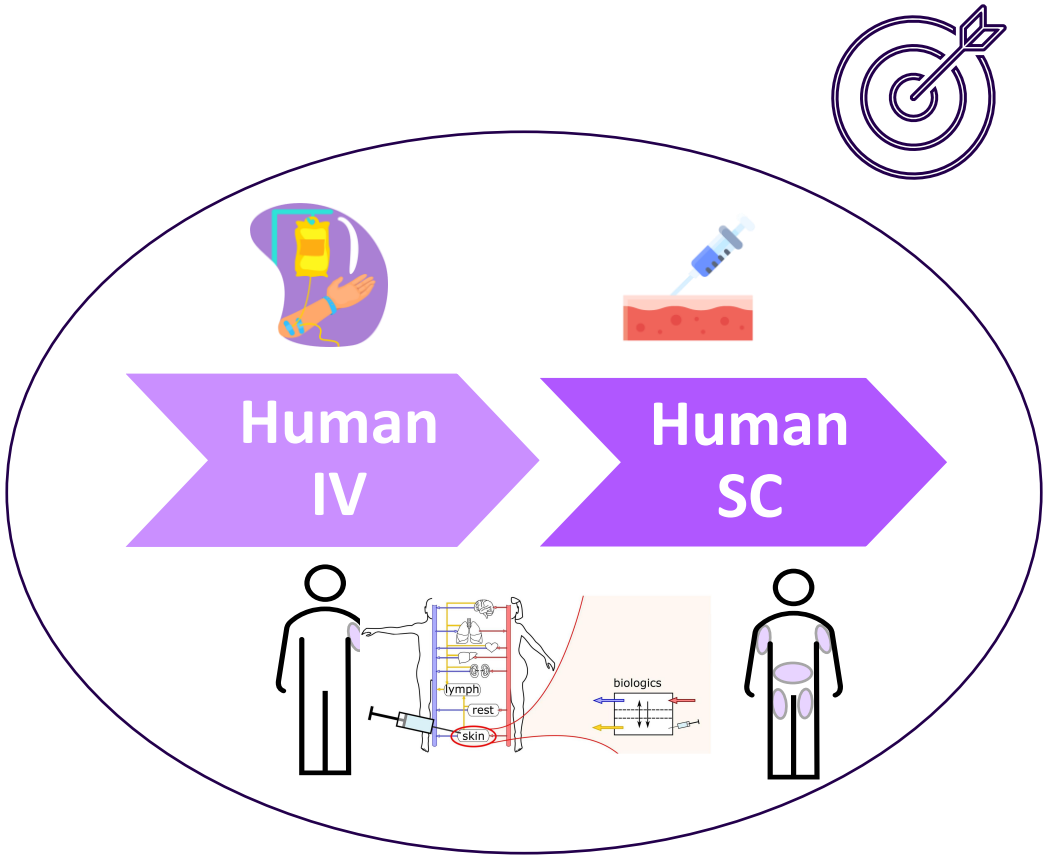

Establish a model-based strategy for predicting mAbs PK in humans (FIH) following SC administration with and without prior data on IV PK

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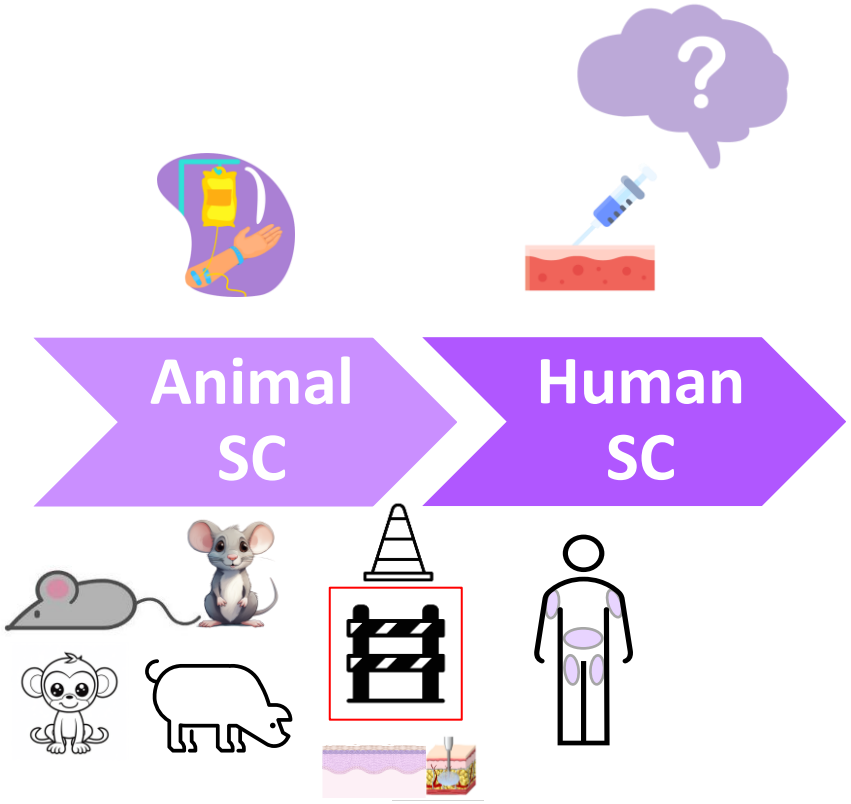

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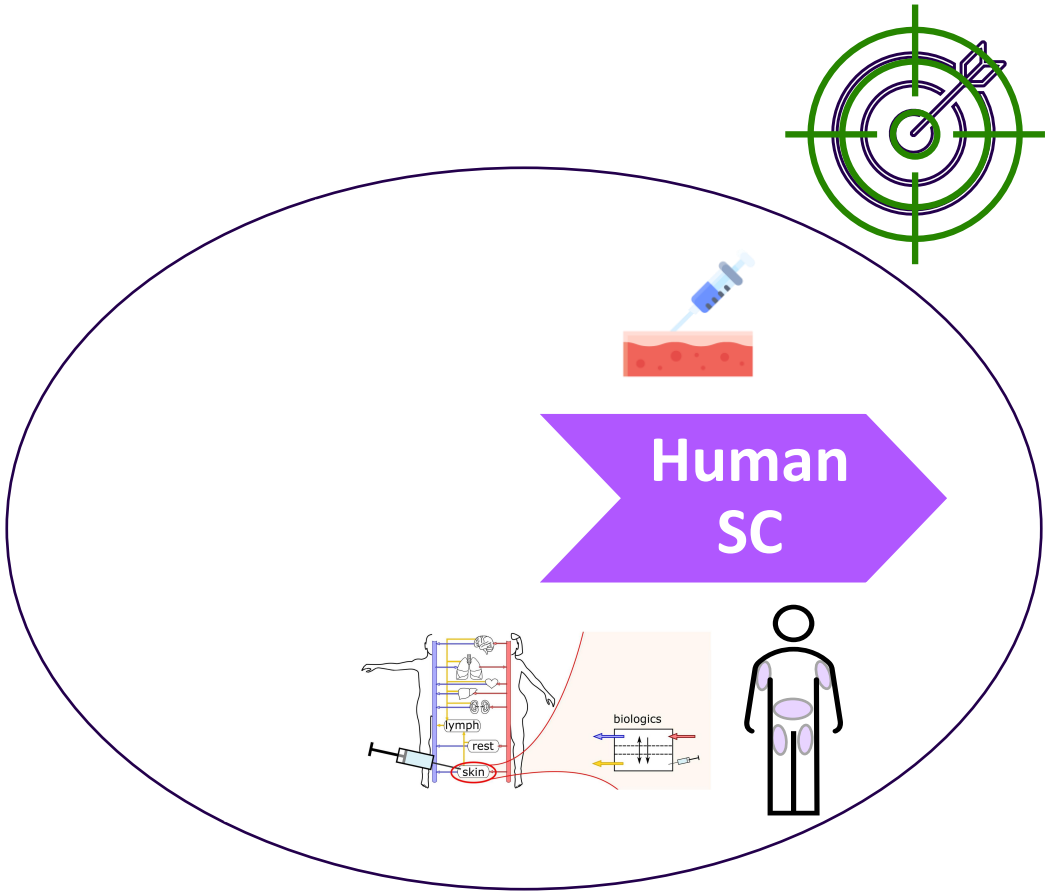

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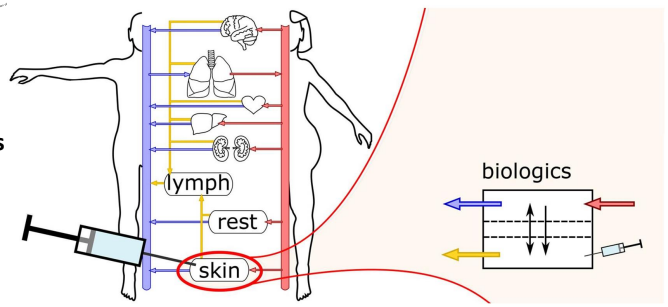
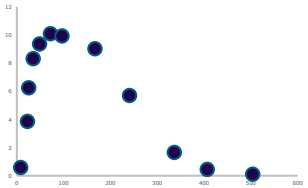
Subcutaneous administration and PBPK modeling

PBPK model for SC administration



Attraction of macrophages
Encapsulation
Tissue damage
Excipients effects
Administration site

Degradation
Off-target binding
Immunogenicity
Absorption
Administration site



Diffusion
Release rate
Concentration
Excipient effects
Formulation effects

Physiology

Species:
- **Disease state**
- **Capillary density**
- **Lymph flow**
- **Blood flow**

SC tissue:
- **Composition**
- **Thickness**
- **Temperature**
- **Interstitial pressure**

Drug

Molecular weight
Molecular size
Shape
Charge
Solubility

Formulation

Aggregation
Injection volume
Injection rate
Viscosity
Stability

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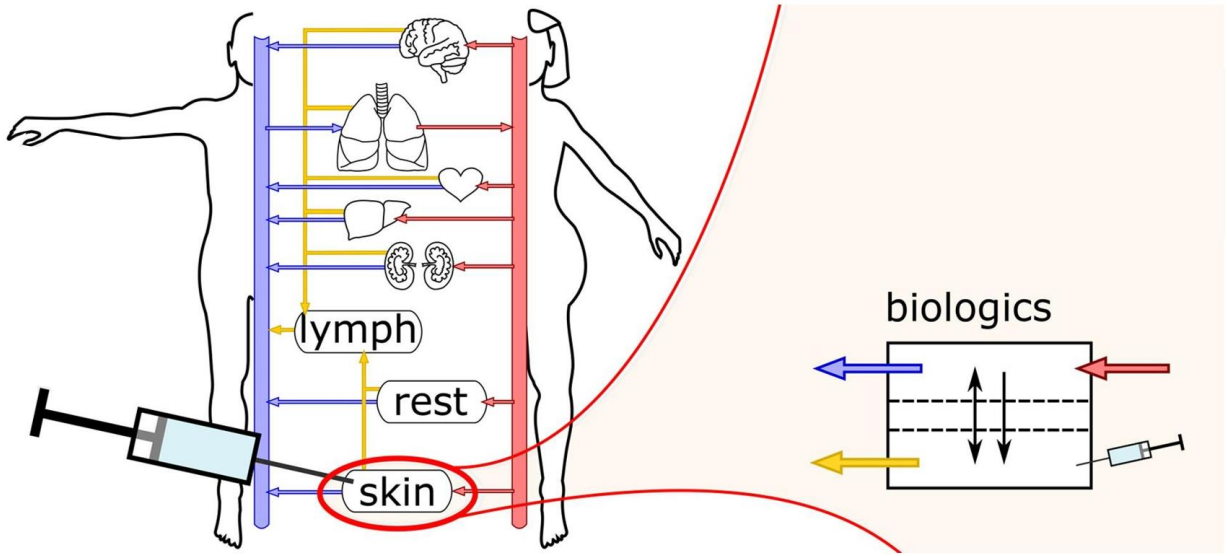
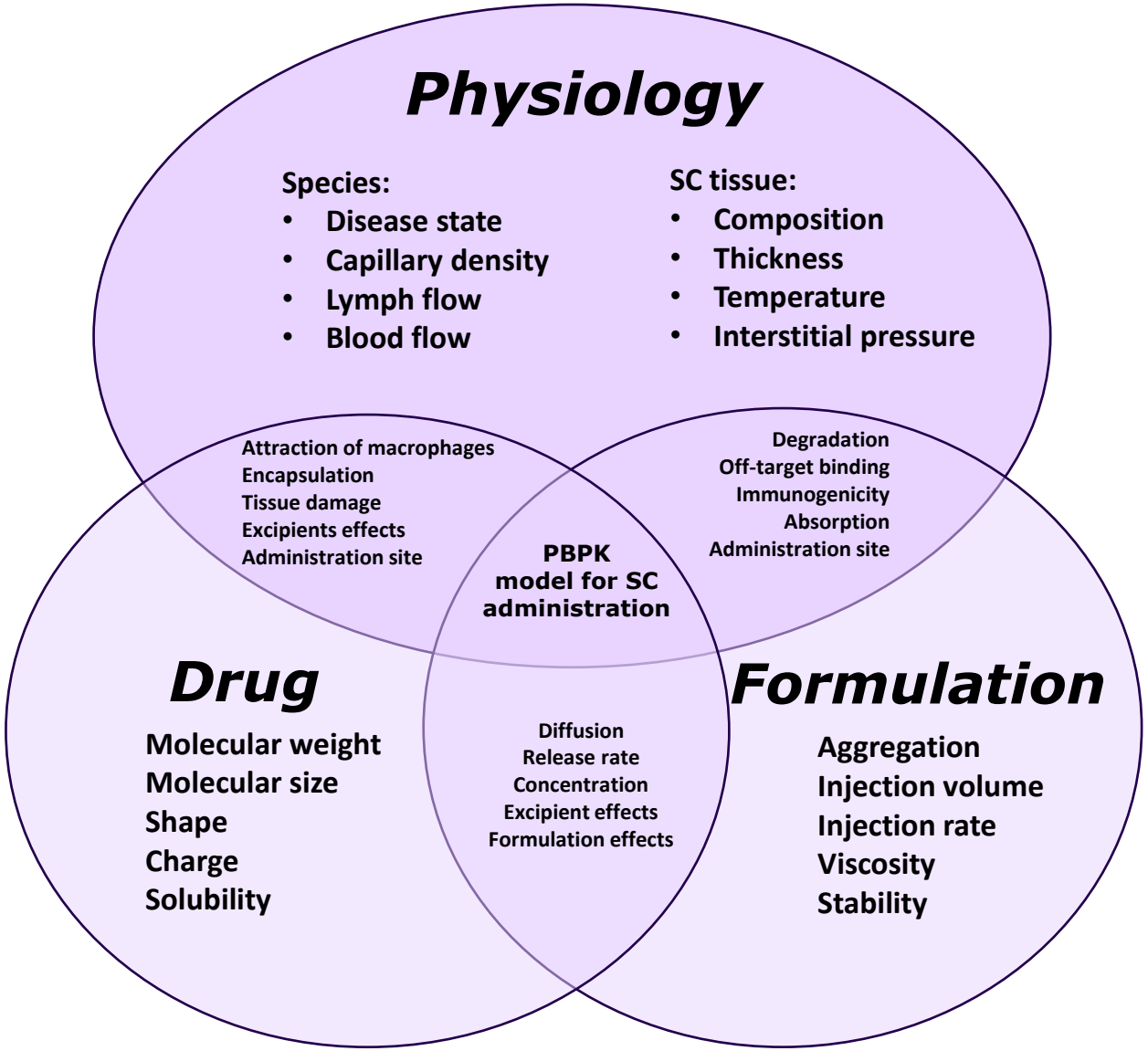
4. Adapted from Dubbelboer IR, Sjögren E., 2022, Physiological based pharmacokinetic and biopharmaceutics modelling of subcutaneously administered compounds–An overview of in silico models

Subcutaneous administration and PBPK modeling





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4. Adapted from Dubbelboer IR, Sjögren E., 2022, Physiological based pharmacokinetic and biopharmaceutics modelling of subcutaneously administered compounds–An overview of in silico models

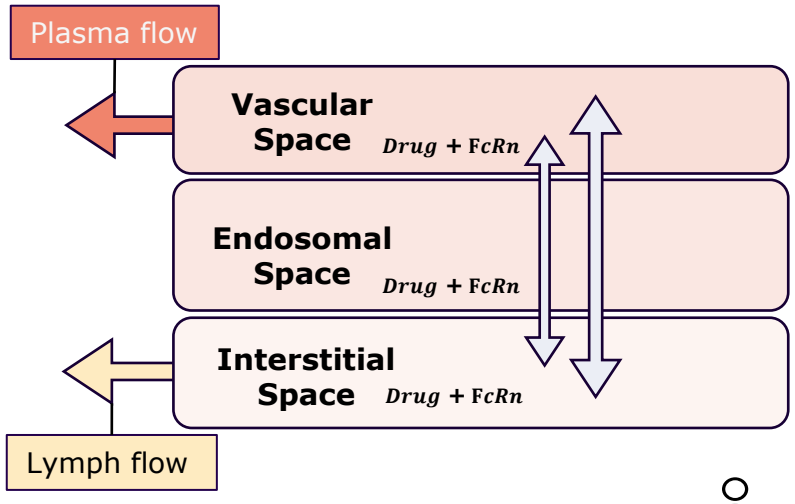
Subcutaneous absorption model

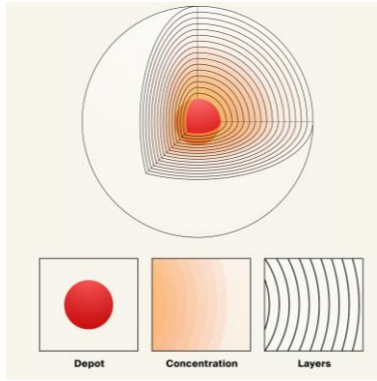
Physiologically based model structure

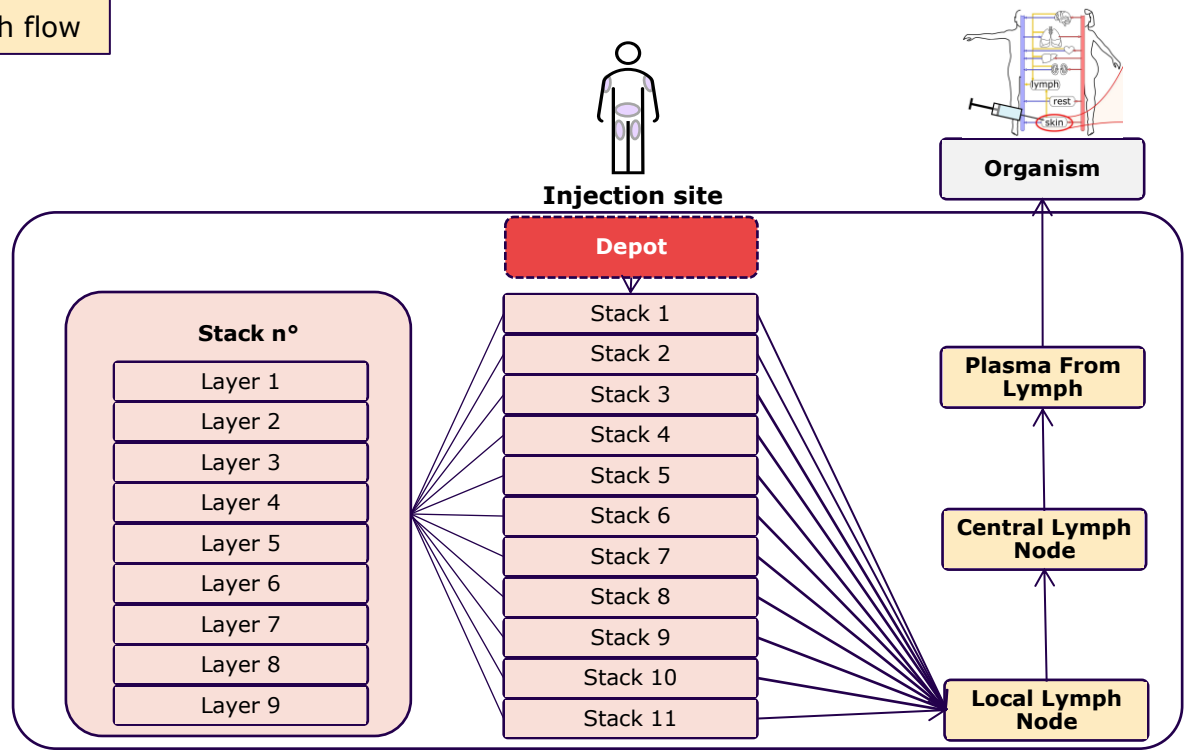
Describe the spatial-temporal drug disposition in the SC tissue (3D)

Model elements

- Depot = Injection
  - Injection volume
  - Injection rate
  - Undissolved drug – particles
- Layers = representing the tissue surrounding the depot
  - Dynamic layer sizing to allow for sufficient space
  - Geometry: sphere or cylinder
- Dispersion in tissue
  - Defined by user
  - 1/3 shells may be filled at administration
- Alignment to OSP PBPK structure
  - Parameterization and structure
  - 2-pore theory for extravasation
  - Endosomal clearance/FcRn-binding







5. Niederalt C et 2018. A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim. J Pharmacokinetics Pharmacodynamics. 2018

Establish a model-based strategy for predicting mAbs PK in humans following SC administration with and without prior data on IV PK

The construction of a reference database used for planned modeling investigations and predictions

1. In vitro drug properties

2. In vivo IV PK data

3. In vivo SC PK data

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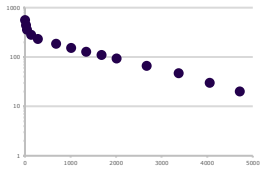
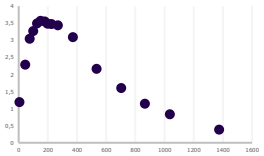
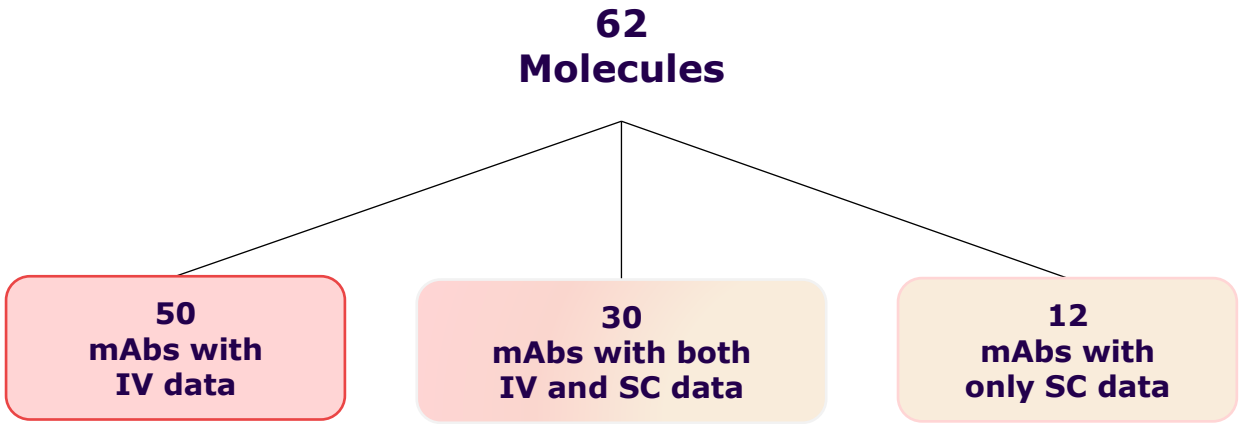


3. In vivo SC PK data



- Criteria for bibliographic search:
  - Monoclonal antibody
  - Drug properties
  - Population characteristics
  - Linear pharmacokinetics
  - IV and SC Data
  - Full time-course available



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Assess the SC absorption model to predict mAbs SC absorption in the context of use for an **IV to SC** clinical switch

1. 30 mAbs IV and SC

2. Individual Kd_{FcRn} estimation

3. SC prediction using individual Kd_{FcRn}

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- In vitro drug properties
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2. Individual Kd_{FcRn} estimation

- Reference IV plasma concentration
- Drug specific Kd_{FcRn} estimation
- Systemic disposition

3. SC prediction using individual Kd_{FcRn}

- Reference SC plasma concentration
- SC PBPK absorption model
- SC PBPK prediction

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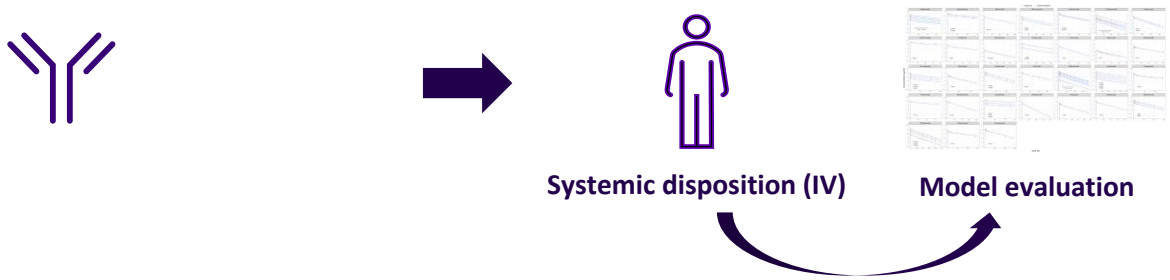

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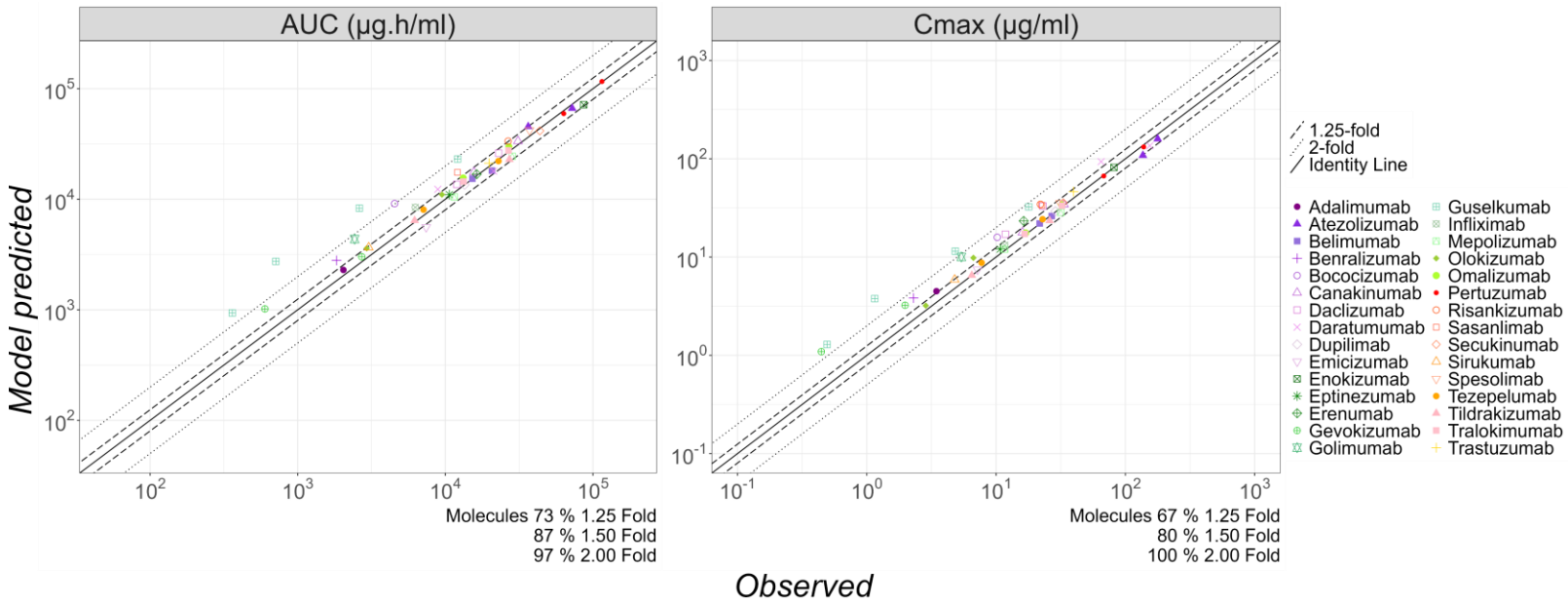
SC PBPK prediction

Good predictive performance of the SC absorption model in the context of a clinical switch from IV to SC



- 29 of 30 mAbs with model predicted AUC and Cmax values within the two-fold (0.50-2.00) range compared to the observed data

✓ The predictive performance of the SC absorption model for switching from IV to SC administration of mAbs was successfully evaluated

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Establish a model-based strategy for predicting mAbs PK in humans following SC administration with and without prior data on IV PK

The construction of a reference database used for planned modeling investigations and predictions	Assess the SC absorption model to predict mAbs SC absorption in the context of use for an **IV to SC** clinical switch	Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after **IV** administration
1. In vitro drug properties	1. 30 mAbs IV and SC	1. 50 mAbs IV
2. In vivo IV PK data	2. Individual Kd_{FcRn} estimation	2. Estimation of the reference Kd_{FcRn} from clinical data
3. In vivo SC PK data	3. SC prediction using individual Kd_{FcRn}	3. Naive PK prediction using the reference Kd_{FcRn} value

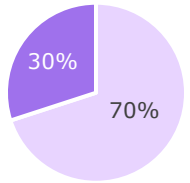
Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after IV administration

1. 50 mAbs IV

Global dataset

Training dataset 35 mAbs

Validation dataset 15 mAbs



2. Estimation of the reference Kd_{FcRn} from clinical data

Training dataset (35)

IV PBPK model building

Drug-specific Kd_{FcRn} estimation

Median of the estimated drug-specific Kd_{FcRn} (reference Kd_{FcRn})

3. Naive PK prediction using the reference Kd_{FcRn} value

Validation dataset (15)

Reference Kd_{FcRn}

IV PBPK model building

IV PBPK prediction and evaluation

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Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after IV administration

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Reference Kd_{FcRn}

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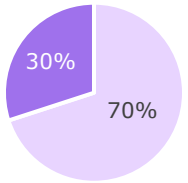

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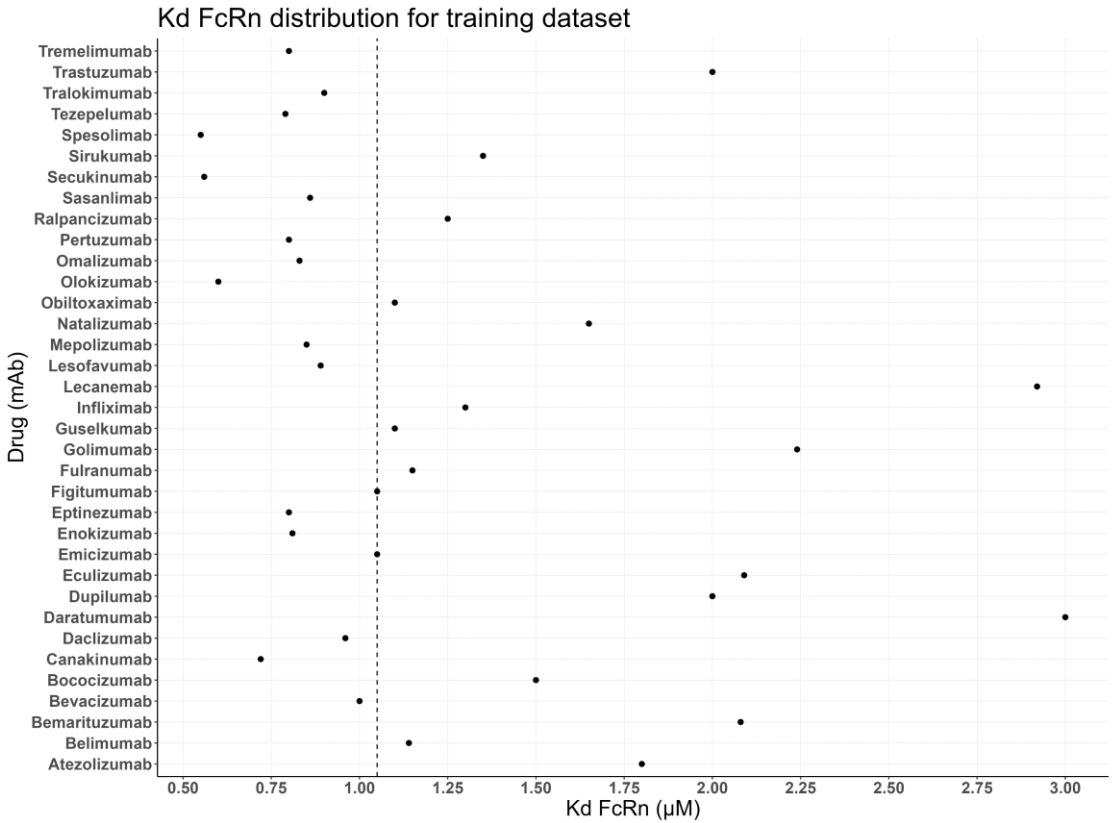
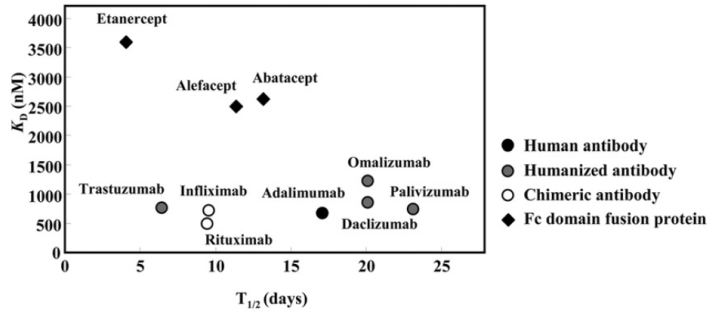
Median of the estimated drug-specific Kd_{FcRn} (reference Kd_{FcRn})





Structure	Nonproprietary name	Binding target	Affinity to FcRn K_D (nM)	Half-life (days)	cited from the literature
Human antibody	Adalimumab	TNFα	672	14.7-19.3	Weisman et al., 2003
Humanized antibody	Daclizumab	CD25	846	20	Vincenti et al., 1998
	Omalizumab	IgE	1237	20	Casale et al., 1997
	Palivizumab	RSV F protein	750	19-27	Subramanian et al., 1998
	Trastuzumab	HER2	773	2.7-10	Tokuda et al., 1999
Chimeric antibody	Infliximab	TNFα	727	9.5	Cornillie et al., 2001
	Rituximab	CD20	508	9.4	Maloney et al., 1997
Mouse antibody	Muromonab-CD3	CD3	ND	0.75	Hooks et al., 1991
Fc-fusion protein	Abatacept	CD80/CD86	2633	13.1	prescribing information
	Alefacept	CD2	2506	11.3	prescribing information
	Etanercept	TNFα	3612	4	Lee et al., 2003

✓ Distribution of estimated Kd_{FcRn} values for the mAbs included in the training dataset (median represented as dashed line)

✓ Kd values of binding between Fc domain-containing therapeutic proteins and human FcRn[7]

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6. Suzuki T, al (2010) Importance of Neonatal FcR in Regulating the Serum Half-Life of Therapeutic Proteins Containing the Fc Domain of Human IgG1: A Comparative Study of the Affinity of Monoclonal Antibodies and Fc-Fusion Proteins to Human Neonatal FcR

Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after IV administration

1. 50 mAbs IV

Global dataset

Training dataset 35 mAbs

Validation dataset 15 mAbs

2. Estimation of the reference Kd_{FcRn} from clinical data

Training dataset (35)

IV PBPK model building

Drug-specific Kd_{FcRn} estimation

Median of the estimated drug-specific Kd_{FcRn} (reference Kd_{FcRn})

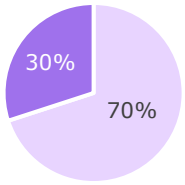
3. Naive PK prediction using the reference Kd_{FcRn} value

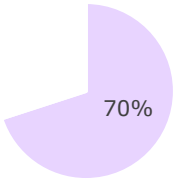
Validation dataset (15)

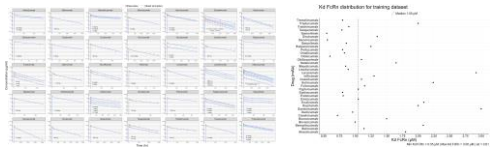
Reference Kd_{FcRn}

IV PBPK model building

IV PBPK prediction and evaluation



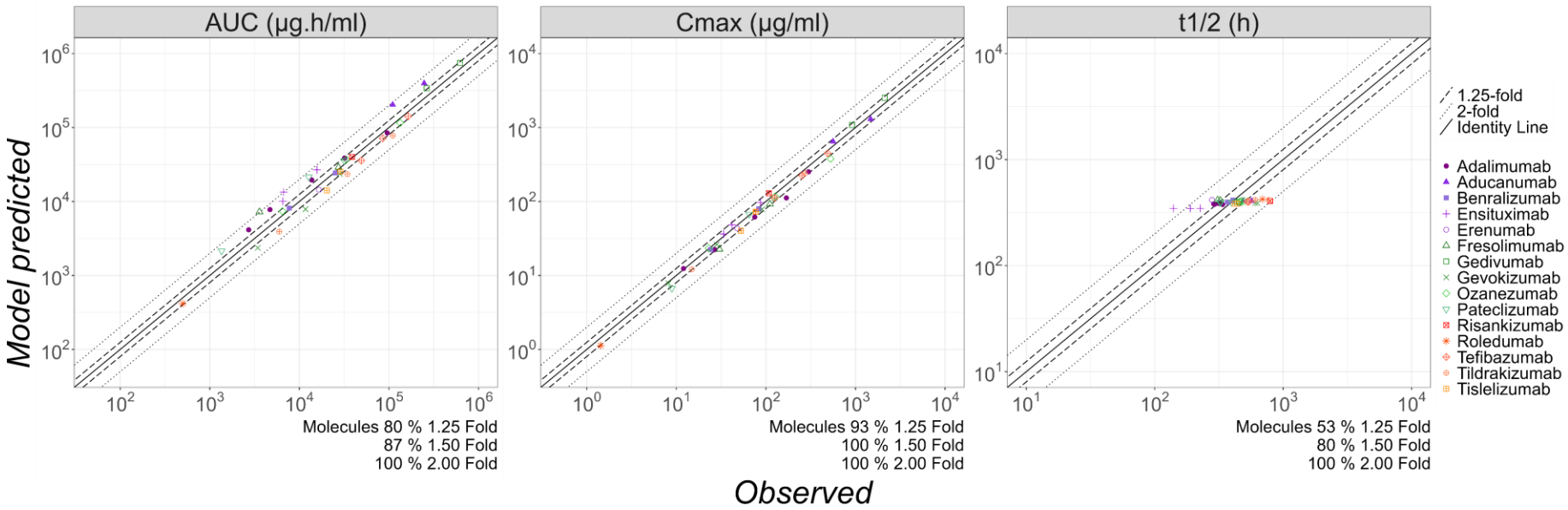




3. Naive PK prediction using the reference Kd_{FcRn} value

IV PBPK prediction and evaluation

Good predictive performance of the reference Kd_{FcRn} value is observed when used to predict mAbs PK



- All 15 mAbs with model predicted AUC, Cmax, and $t_{1/2}$ values within the two-fold (0.50-2.00) range compared to the observed data

✓ This median value was considered as a reference value for Kd_{FcRn}

Establish a model-based strategy for predicting mAbs PK in humans following SC administration with and without prior data on IV PK

The construction of a reference database used for planned modeling investigations and predictions	Assess the SC absorption model to predict mAbs SC absorption in the context of use for an **IV to SC** clinical switch	Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after **IV** administration	Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after **SC** administration
1. In vitro drug properties	1. 30 mAbs IV and SC	1. 50 mAbs IV	1. Identification of variability in SC absorption (30 mAbs)
2. In vivo IV PK data	2. Individual Kd_{FcRn} estimation	2. Estimation of the reference Kd_{FcRn} from clinical data	2. 12 mAbs SC
3. In vivo SC PK data	3. SC prediction using individual Kd_{FcRn}	3. Naive PK prediction using the reference Kd_{FcRn} value	3. SC PBPK prediction using the reference Kd_{FcRn} and variability SAEM estimates

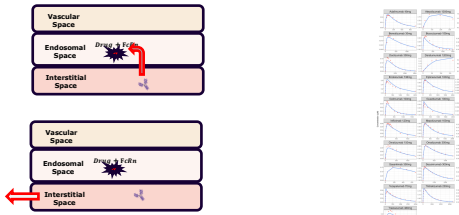
Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after SC administration

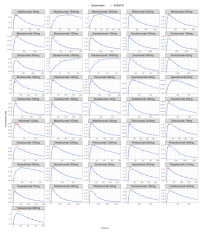
1. Identification of variability in SC absorption (30 mAbs)

Key process for SC

Individual fit with SAEM (30 mAbs IV and SC)

Parameter estimates from SAEM





2. 12 mAbs SC

In vitro drug properties

In vivo SC PK

No prior data on IV PK

3. SC PBPK prediction using the reference Kd_{FcRn} and variability SAEM estimates

Reference Kd_{FcRn}

Variability SAEM estimates

Naïve SC PBPK prediction

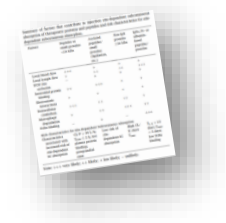
1. Identification of variability in SC absorption (30 mAbs)

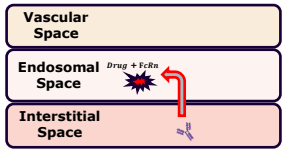
Key process for SC

Individual fit with SAEM (30 mAbs IV and SC)

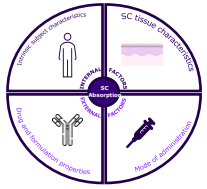
Parameter estimates from SAEM

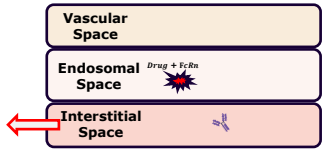
Injection site endosomal clearance

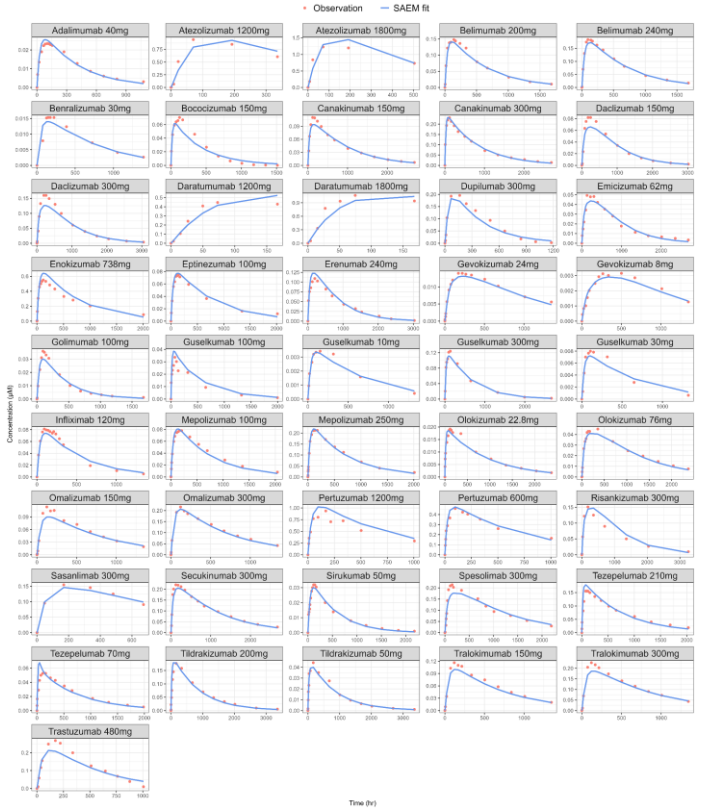




Injection site lymph flow transport







Parameter	Estimate	RSE (%)	p-value
Lymph flow proportionality factor	0.0075	Fixed	-
Rate constant for endosomal uptake (1/min)	0.7409	18	-
beta_DOSE (Rate constant for endosomal uptake)	-0.0016	35	0.002
IIV Lymph flow proportionality factor (%)	69	23	-
IIV Rate constant for endosomal uptake (%)	75	26	-
Proportional residual error	0.1420	5	-
Additive residual error (μM)	0.0029	6	-

✓ In order to integrate variability in the absorption phase, these parameters with their inter-mAbs variability were estimated using SAEM algorithm coupled with the WB-PBPK model

7. Teutonico et al 2024. Estimation of population parameter values and variability coupling non-linear mixed-effects modeling (based on SAEM algorithm) with a whole-body PBPK model. PAGE meeting 32 Abstract 11055
8. Comets et al 2017. Parameter Estimation in Nonlinear Mixed Effect Models Using saemix, an R Implementation of the SAEM Algorithm. Journal of Statistical Software

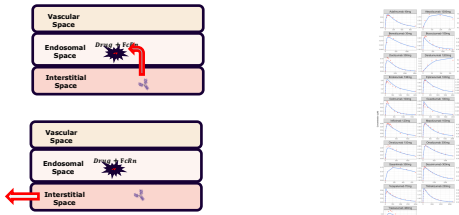
Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after SC administration

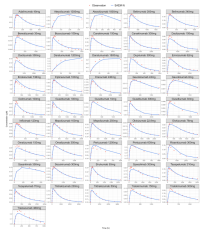
1. Identification of variability in SC absorption (30 mAbs)

Key process for SC

Individual fit with SAEM (30 mAbs IV and SC)

Parameter estimates from SAEM





2. 12 mAbs SC

In vitro drug properties

In vivo SC PK

No prior data on IV PK

3. SC PBPK prediction using the reference Kd_{FcRn} and variability SAEM estimates

Reference Kd_{FcRn}

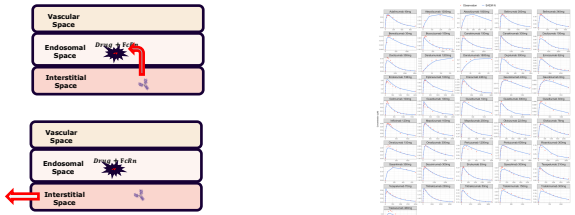
Variability SAEM estimates

Naïve SC PBPK prediction

Establish an approach for naïve PBPK model-based predictions of clinical PK of mAbs after SC administration

1. Identification of variability in SC absorption (30 mAbs)

- Key process for SC
- Individual fit with SAEM (30 mAbs IV and SC)
- Parameter estimates from SAEM



2. 12 mAbs SC

- In vitro drug properties
- In vivo SC PK
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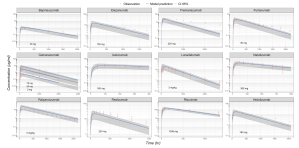
- Reference Kd_{FcRn}
- Variability SAEM estimates
- Naïve SC PBPK prediction



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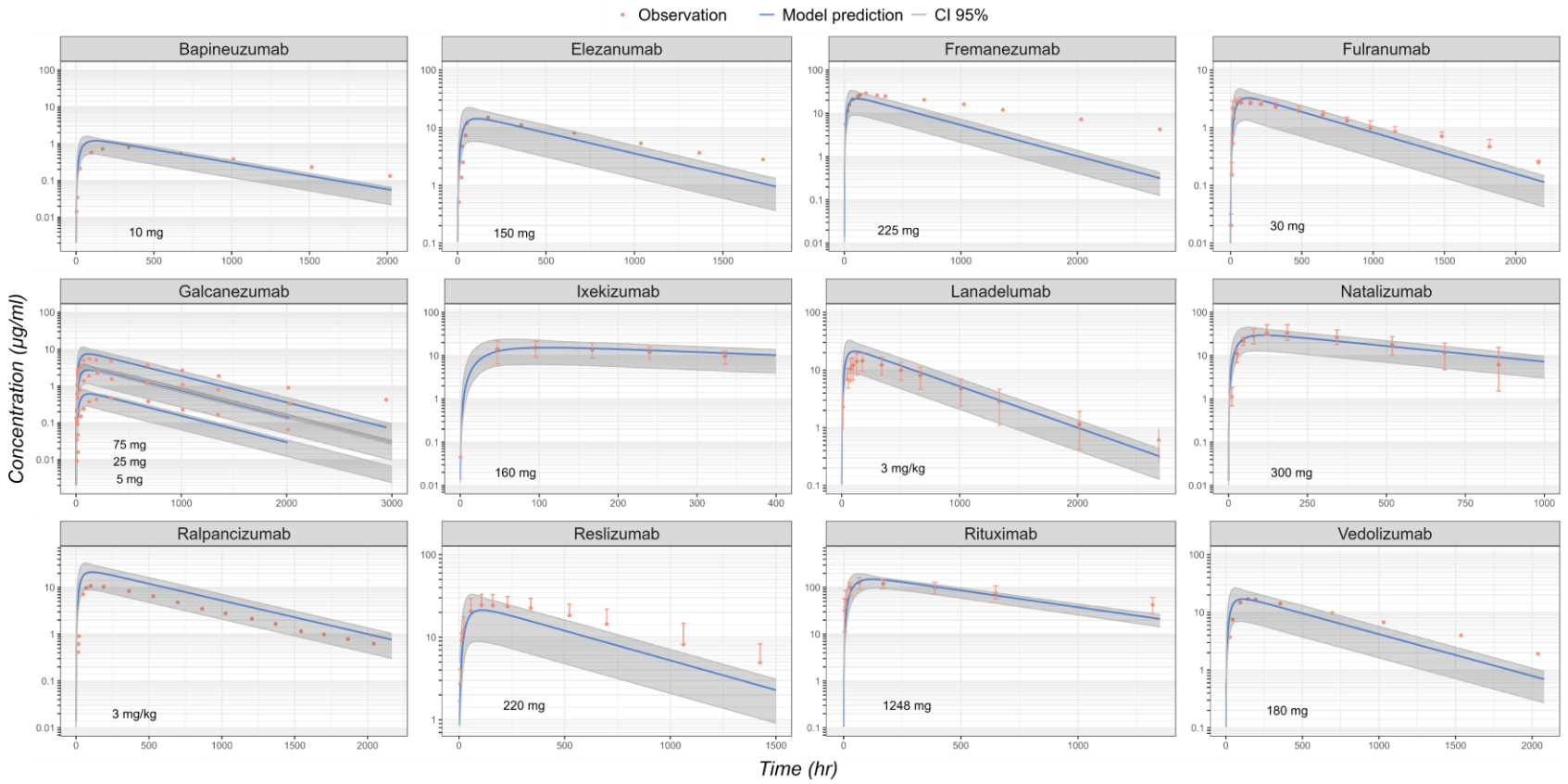
3. SC PBPK prediction using the reference Kd_{FcRn} and variability SAEM estimates

Naïve SC PBPK prediction



- The WB-PBPK model
- The SC absorption module
- Pop WB-PBPK approach for parameter estimates and inter-mAbs variability
- Reference value for human Kd_{FcRn}

✓ The absorption falls within the prediction interval for most of the mAbs included in the database

Establish a model-based strategy for predicting mAbs PK in humans following SC administration with and without prior data on IV PK

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Conclusion

This approach provides a PBPK framework for predicting human PK of mAbs based on FcRn affinity, in order to support drug development and FIH trials.

The results align well with FDA’s plan to phase out animal testing for mAbs, where it is possible to achieve reliable results using modeling and simulations.

Local SC processes, including interstitial retention and endosomal uptake, were identified as key areas for further investigation in relation to mAbs properties (formulation, physicochemical parameters).

Further perspectives include the validation with mAbs incorporating specific mechanisms such as target-mediated drug disposition (TMDD) and anti-drug antibodies (ADA).

Acknowledgements

- Sanofi, Translational Medicine Unit (TMU), Quantitative Pharmacology, Vitry-Sur-Seine, France: Donato Teutonico, Antoine Deslandes, Laurent Nguyen.

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Thank you for your attention

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