PQRI BTC 2020 Webinar Series

Biopharmaceutics of mAbs: Fundamentals and Pharmaceutical Development Aspects

Moderator: Filippos Kesisoglou, Ph.D., Merck & Co., Inc.
Presenters: Mikolaj Milewski, Ph.D., Merck & Co., Inc.
Jingtao Zhang, Ph.D., Merck & Co., Inc.

December 2020

Agenda and Abstract

I. Welcome and Overview of Webinar

Moderator: Filippos Kesisoglou, Ph.D.

II. Biopharmaceutics of mAbs: Fundamentals and Pharmaceutical Development Aspects

Presenters: Mikolaj Milewski, Ph.D. and Jingtao Zhang, Ph.D.

III. Moderated Q&A Session with the speakers

Abstract: Last decade witnessed the rapid increase in regulatory approvals of monoclonal antibody (mAb) therapeutics, as well as its sustained success in the commercial market. The product development, mode of administration, safety/immunogenecity, and biopharmaceutics of biologics are all areas where multiple differences can be observed as compared to small molecule therapeutics. This presentation will highlight the fundamentals of mAb drug products including overall structure and ADME properties and discuss several biopharmaceutical aspects of drug product development contributing to its therapeutic success. Specifically, drivers for introducing subcutaneous formulations as opposed to intravenous counterparts, use of hyaluronidase as a subcutaneous injection dispersion enhancer, formulation and device bridging for subcutaneous injection, and historical experience with preclinical-to-clinical translation of subcutaneous bioavailability will be discussed with specific examples. A thorough understanding of biopharmaceutics aspects of mA product development can greatly facilitate seamless drug formulation and device development, design of preclinical and clinical studies, and commercial manufacturing of a sterile drug product.

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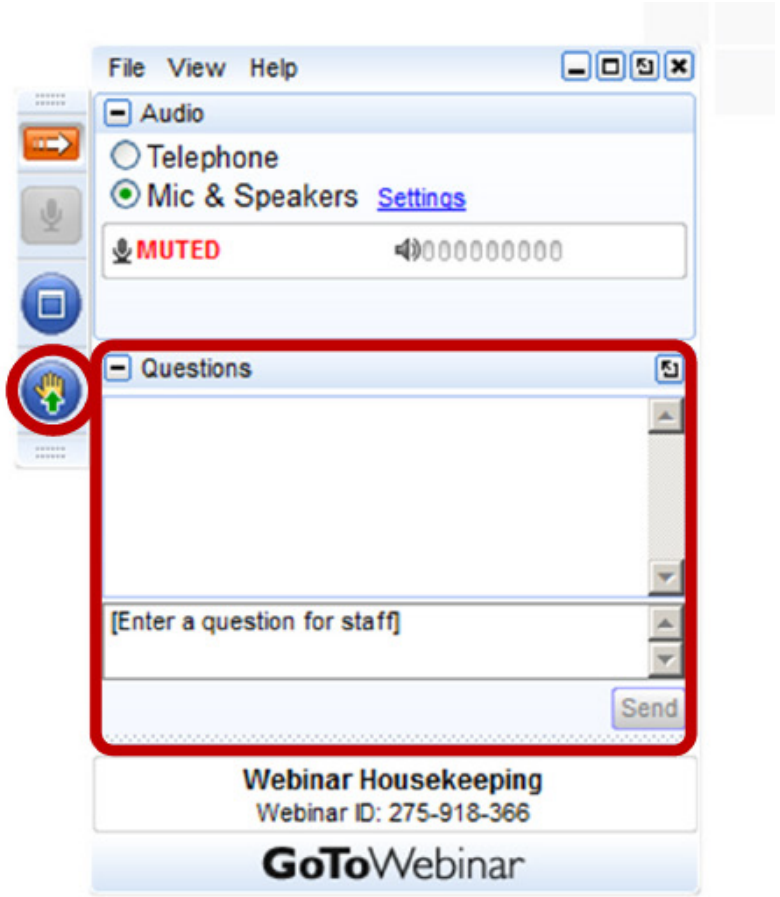

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- Unites thought leaders from regulatory agencies, standard setting bodies, industry and academia to conduct research and share knowledge on emerging scientific and regulatory quality challenges
- Provides a unique, neutral forum to develop broad consensus among a diverse collection of industry organizations and regulatory bodies
- Creates opportunities to accomplish mutual goals that cannot be achieved by individual organizations
- Impacts global regulatory guidance and standards, bringing maximum value to members and patients

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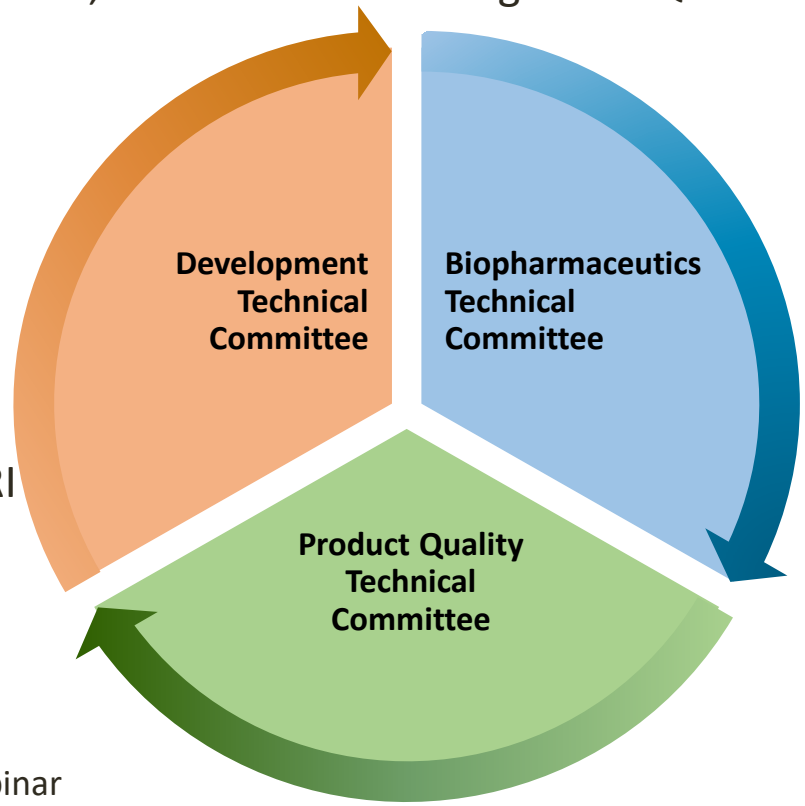

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2020 Webinars

- ***Regulatory Requirements and Scientific Considerations for Biosimilar Products (September 16, 2020)*** Presenters: Stacey Ricci, M.Eng., Sc.D, FDA; Leah Christl, Amgen; Sundar Ramanan, Ph.D., MBA, BioCon

- ***BTC/PQTC Webinar Series: Excipient Considerations for Parenteral Drug Development (July 29, 2020)*** Presenters: Janeen Skutnik-Wilkinson (Biogen) and Thomas Tice, Ph.D., Evonik

- ***The Challenge and the Promise: Developing Complex Drug Products (April 28, 2020)*** Presenters: Wenlei Jiang, Ph.D., FDA and Adrian Goodey, Ph.D., Merck

2019 Webinars

- ***The Expanding IVIVC Toolbox to Enable Drug Product Quality and Clinical Pharmacology – Complementary Traditional and PBPK Based Approaches (June 7, 2019)*** Presenters: Xianyuan (Susie) Zhang, Ph.D., FDA and Filippos Kesisoglou, Ph.D., Merck

- ***Holistic QbD to Enable Product Quality Webinar (October 10, 2019)*** *Presenters:* Ajit Narang, Ph.D., Genentech; Rakhi Shah, Ph.D., FDA; Xavier Pepin, Pharm.D, Ph.D; Divyakant Desai, Ph.D., BMS; Xavier Pepin, Pharm.D, Ph.D., AstraZeneca

Today's Presenters

Mikolaj Milewski, Ph.D., Principal Scientist

Merck & Co., Inc.

mikolaj.milewski@merck.com

Mikolaj Milewski is a Principal Scientist in the Pharmaceutical Sciences department with 9+ years of industrial pharmaceutical research experience. He assesses biopharmaceutics risk of clinical formulations for small-molecule oral programs and large-molecule injectable programs through use of in vitro, in silico, and in vivo methods. Additionally, his responsibilities include valuating feasibility of alternative drug delivery routes for new chemical entities and existing products. His areas of interest are oral and parenteral formulations, drug delivery systems, and biopharmaceutics. Prior to joining Merck Mikolaj earned his PhD degree in Pharmaceutical Sciences in Dr. Audra Stinchcomb's laboratory from the University of Kentucky in Lexington. Mikolaj has authored multiple research and review articles in peer-reviewed journals. He is an active member of AAPS and the Subcutaneous Drug Delivery and Development Consortium.

Today's Presenters

Jingtao Zhang, Ph.D., Principal Scientist
Merck & Co., Inc.
jingtao_zhang@merck.com

Dr. Jingtao Zhang is a principal scientist in the Department of Pharmaceutical Sciences of Merck & Co., Inc., (Kenilworth, NJ). He has more than 13 years' experiences in discovering and developing diverse range of pharmaceuticals including RNAs, conjugates, small molecules, peptides, proteins, and most recently monoclonal antibodies. His past and current roles span across preformulation/characterization, formulation research, and analytical development in early and late phase CMC development. His current research lies in high concentration protein behavior, subcutaneous delivery, and protein instability mechanisms. Prior to Merck, he received his Ph.D. in Chemical Engineering from the University of Wisconsin-Madison. He authored/co-authored more than 30 articles in peer-reviewed journals and delivered more than 30 presentations in national and international conferences.

Biopharmaceutics of mAbs: Fundamentals and Pharmaceutical Development Aspects

Jingtao Zhang & Mikolaj Milewski

Department of Pharmaceutical Sciences

Merck & Co., Inc. Kenilworth, NJ

PQRI presentation, Dec 9th 2020

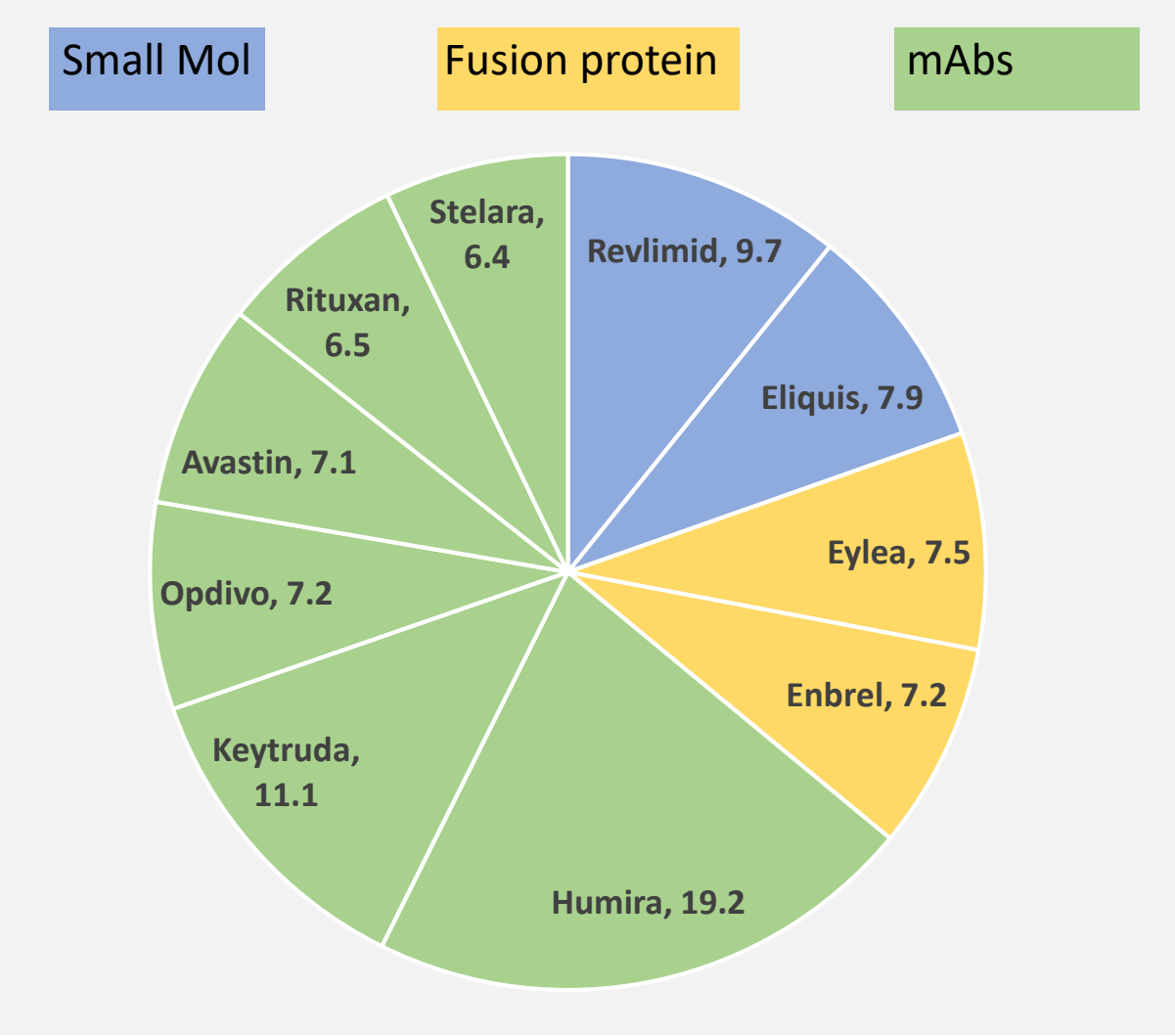
Outline

- mAb fundamentals
  - Products on the market
  - mAb structure
  - ADME
- Biopharmaceutics aspects
  - Intravenous (IV) to subcutaneous (SC) switch
  - Hyaluronidase as dispersion enhancer for SC injections
  - Formulation bridging
  - Preclinical to clinical translation
- Open questions

mAb fundamentals

Monoclonal Antibody Drugs Contribute Greatly to Human Health and will Continue to Grow

2019 Top 10 Best Selling Drugs Globally (US$ Billions)



"The global therapeutic monoclonal antibody market was valued at approximately US$115.2 billion in 2018 and is expected to generate revenue of $150 billion by the end of 2019 and $300 billion by 2025"

Lu et al. Journal of Biomedical Science (2020) 27:1

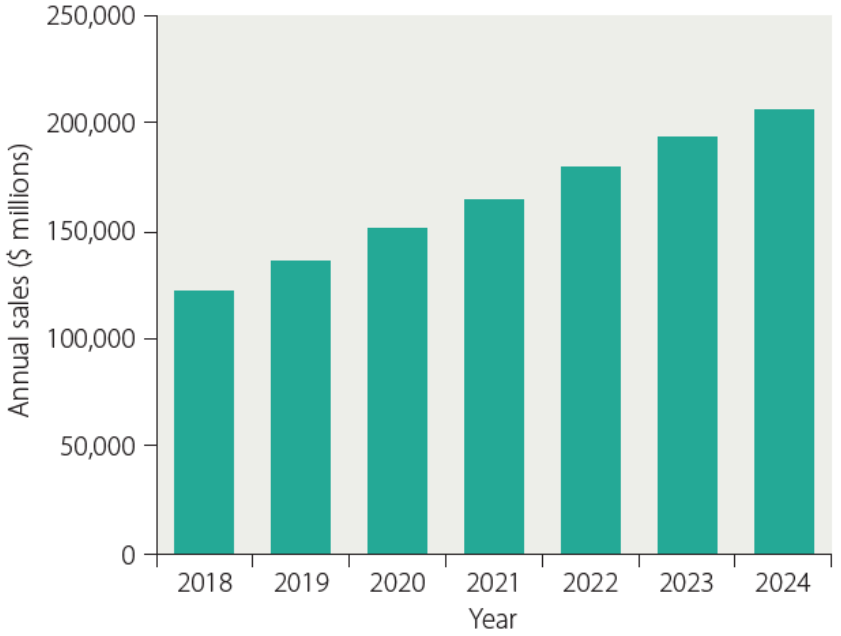
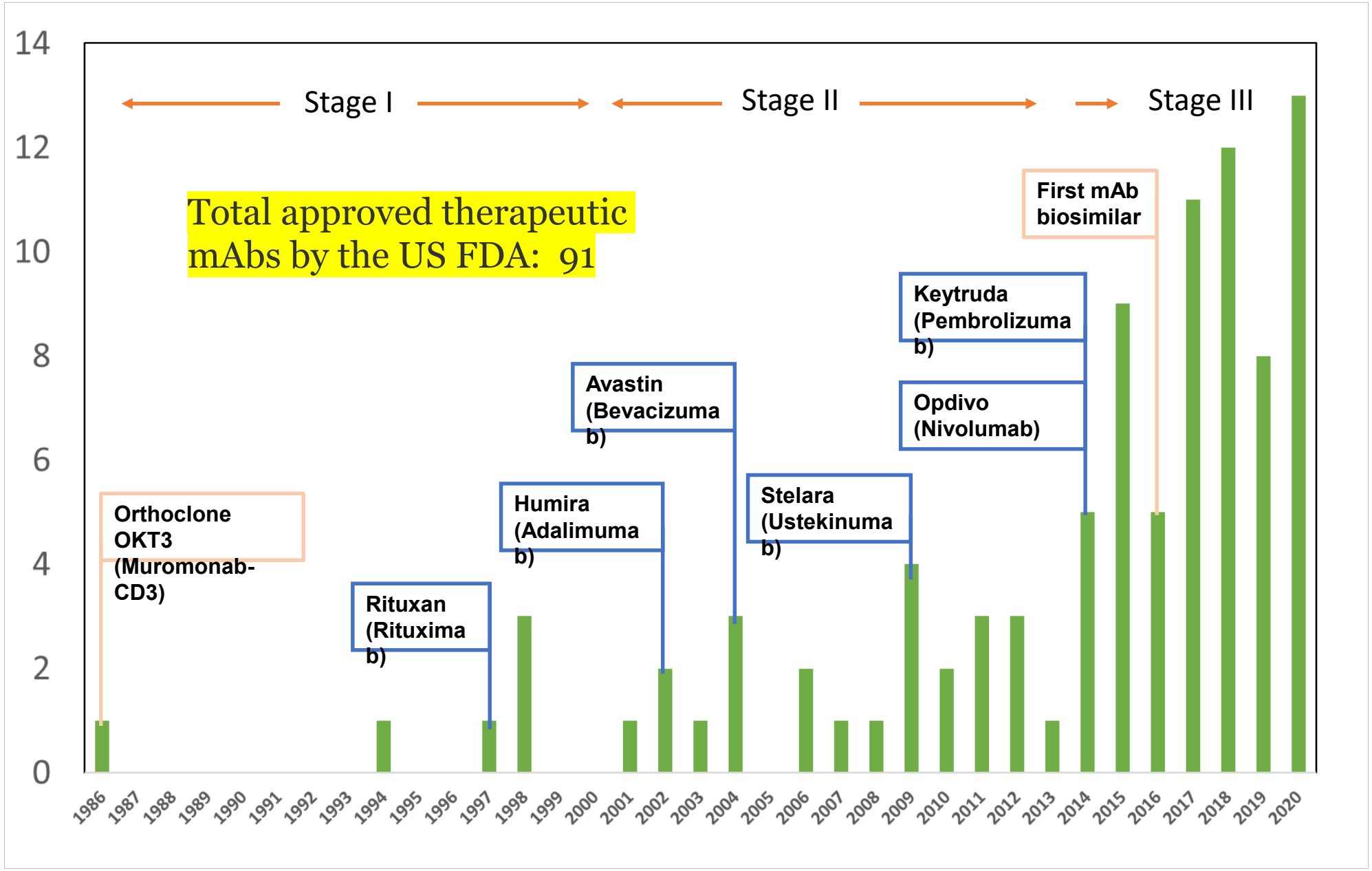


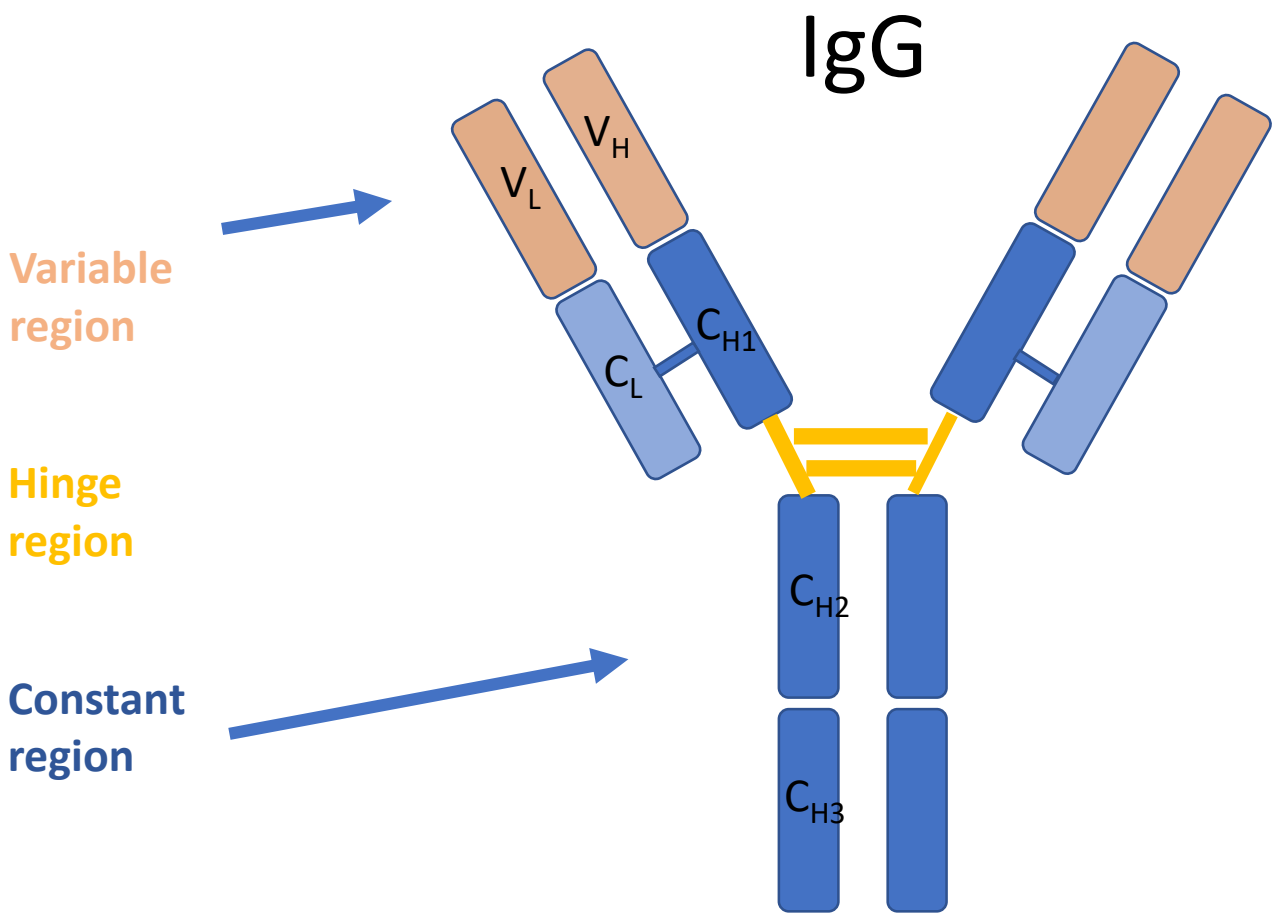
Fig. 1 | Growth in the global sales of monoclonal antibodies from 2018 to 2024. Source: EvaluatePharma, July 2019.

History of Monoclonal Antibody Therapeutics Approval



Data courtesy of the Antibody Society

mAb 101



Fab: fragment antigen binding

- Recognition (antigen binding domain)
- Determines affinity and specificity

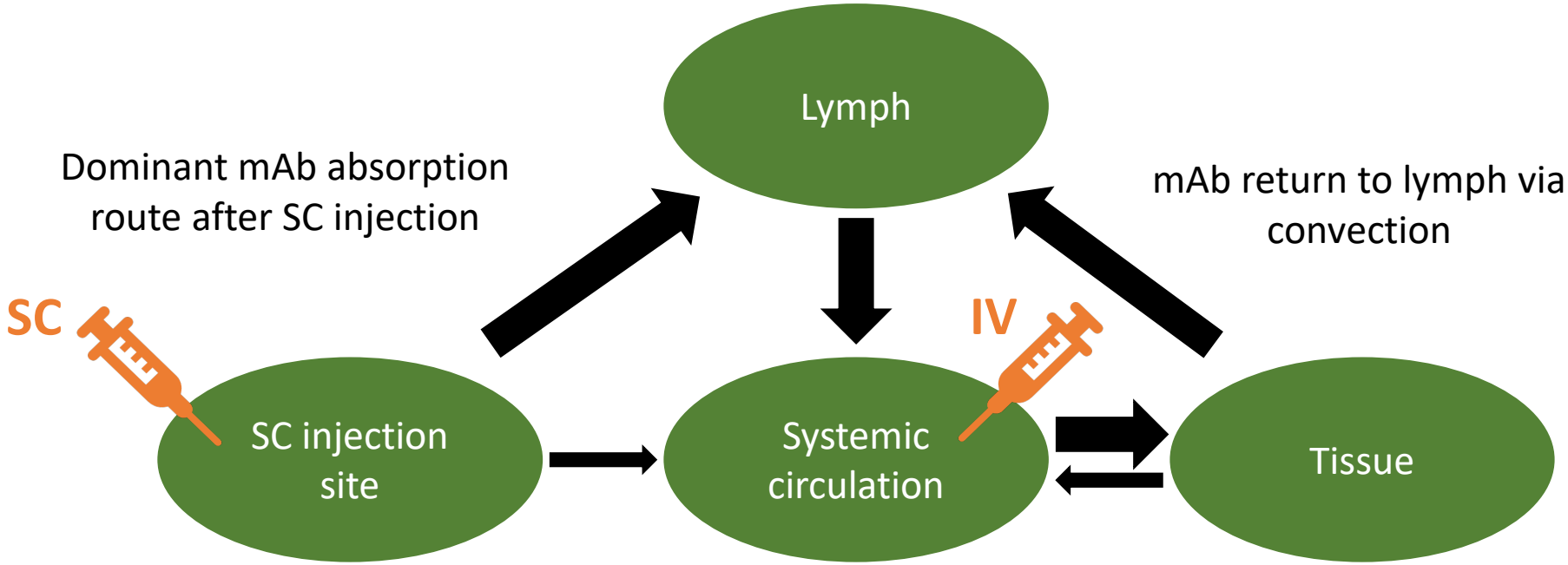
Fc: fragment crystallizable

- mediate immune function (FcγR, C1q)
- determines in vivo half-life (FcRn)

~10 nm (D_H)

~1340 aa, ~150 kDa, PI (4~9)

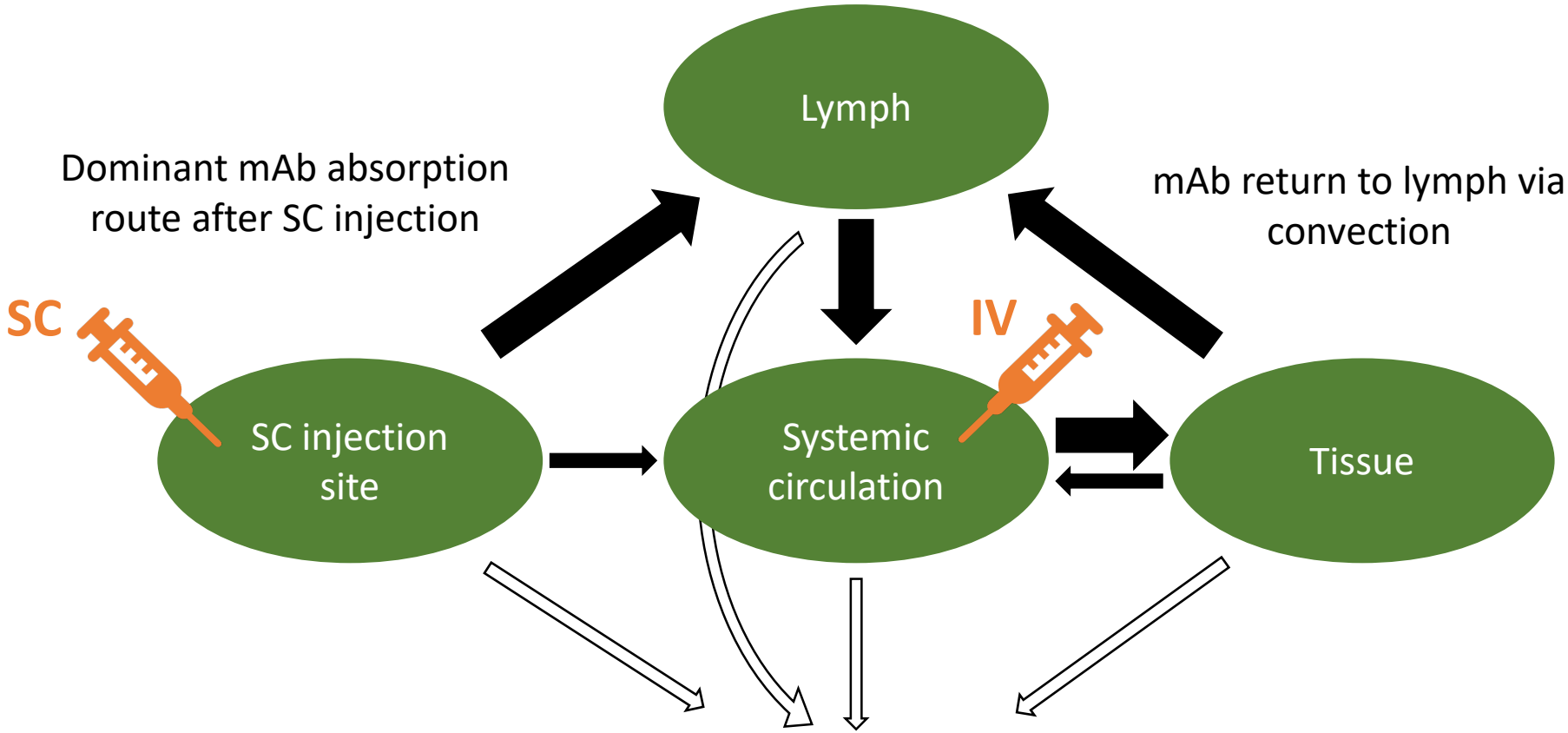
ADME



- Absorption from SC tissue mainly through convective lymphatic uptake
- Long plasma elimination half-lives (3 weeks typical for IgG1, IgG3, and IgG4)
- Distribution by convective extravasation rather than diffusion
- Binding of mAbs: receptors, anti-drug antibodies, FcRn

Adapted from Cephalalgia 2019 Sep; 39(10):1284-1297

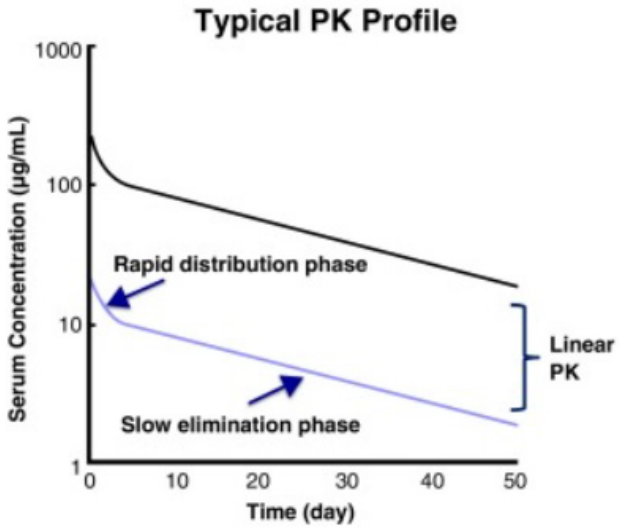
ADME

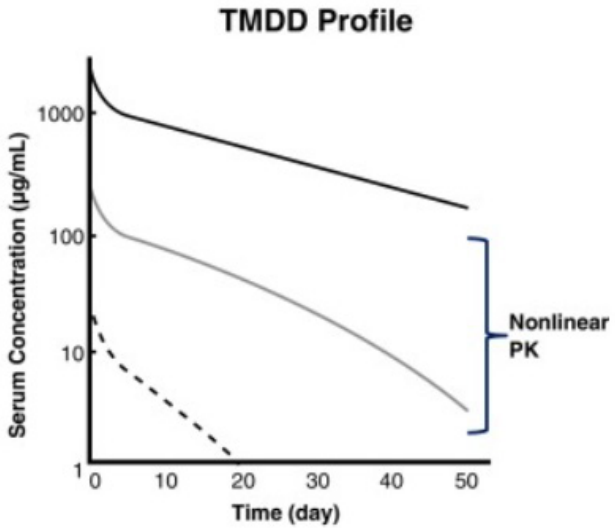


mAb elimination through metabolic degradation, antigen binding, or irreversible tissue binding. Elimination predominantly by same catabolic pathways as endogenous proteins (degraded to amino acid). Negligible non-metabolic elimination.

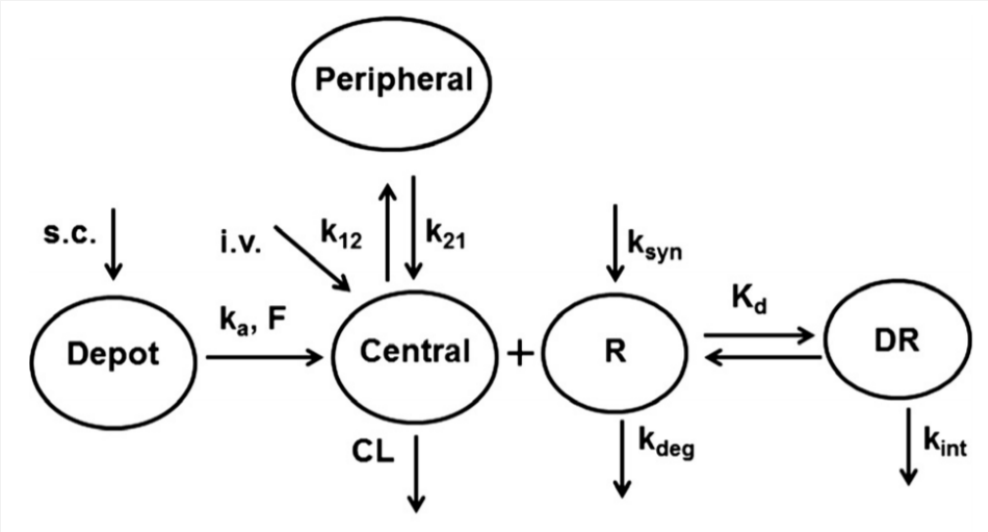
Adapted from Cephalalgia 2019 Sep; 39(10):1284-1297

Drug - pharmacologic target interaction



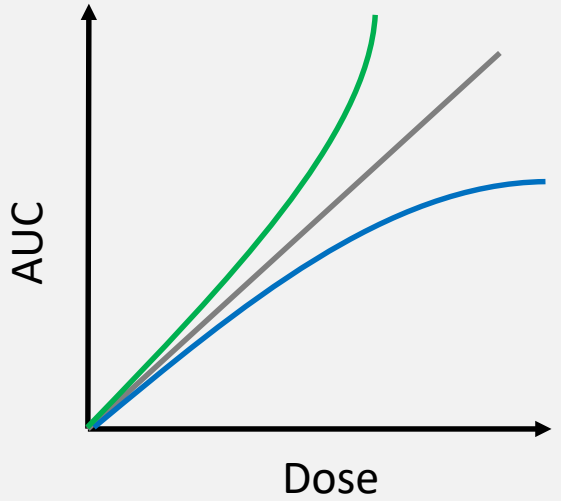


TMDD: target-mediated drug disposition



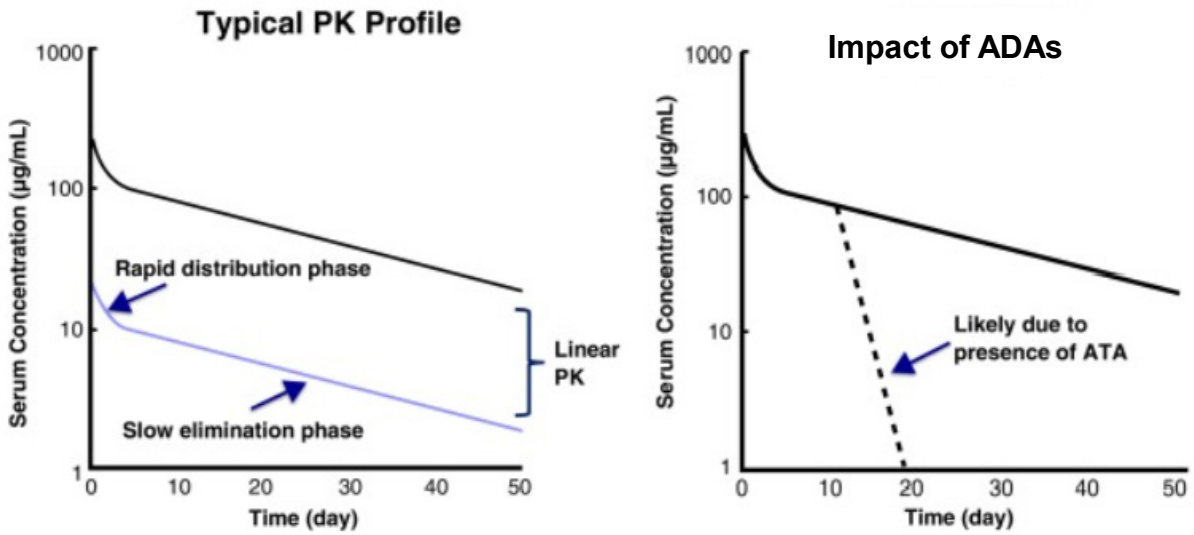
Pharmacol Res Perspect. 2015 Feb; 3(1): e00098.

Drug – receptor interaction can become important for distribution and elimination from the law of mass action perspective



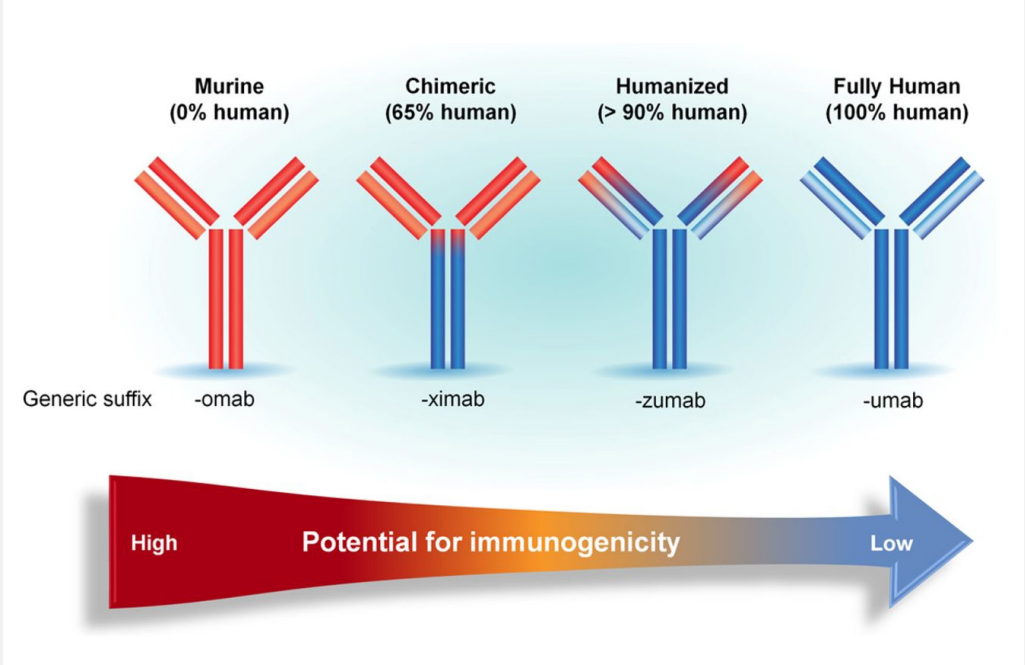
Drug Discovery Today: Technologies
Volumes 21–22, September–December 2016, Pages 75-83

Anti-drug antibodies



Overall, mAbs well tolerated in humans despite containing sequences that may be recognized by the recipient as non-self epitopes and can stimulate an immune response

Drug Discovery Today: Technologies
Volumes 21–22, September–December 2016, Pages 75-83



Circulation 2013 Jun 4;127(22):2222-30.

ADAs (anti-drug antibodies) formation from immune-mediated responses can have a major impact on mAb clearance and efficacy/safety. **When ADAs are present mAb concentrations can suddenly drop due to increased clearance of the immune complexes.**

[Bendtzen, K. Immunogenicity of Anti-TNF-alpha Biotherapies: II. Clinical Relevance of Methods Used for Anti-Drug Antibody Detection. Front Immunol. 6, 109 (2015)]

Neonatal Fc receptor (FcRn)

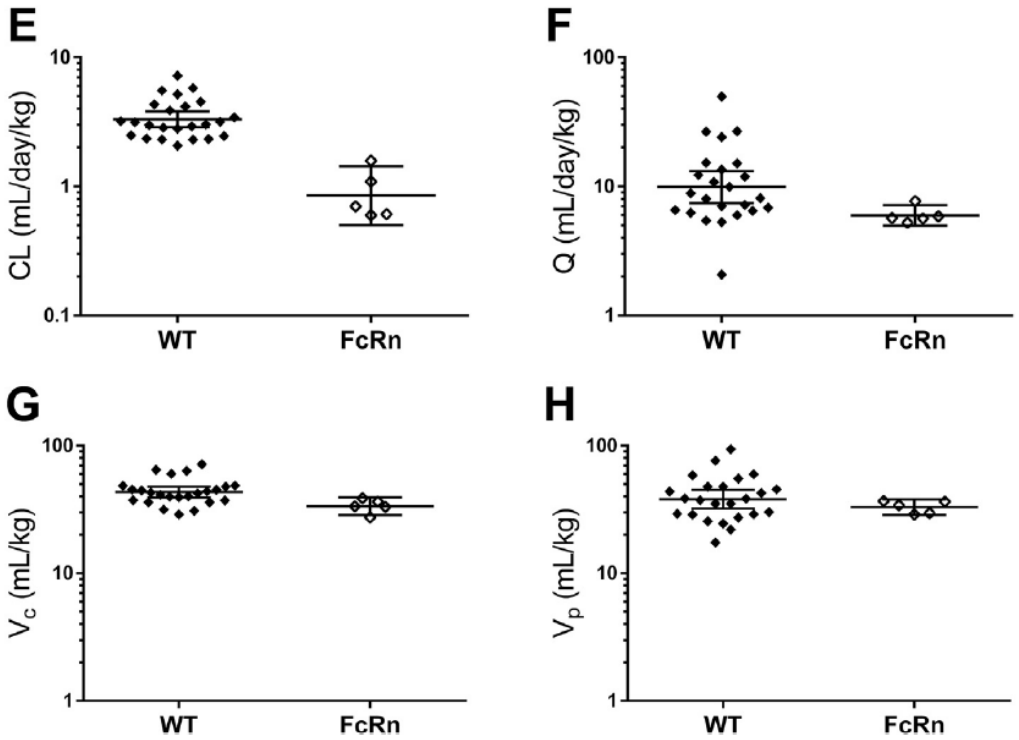


Figure 5. Distribution of CL, Q, Vc, and Vp for mAbs with (FcRn) or without (WT) **mutations to increase the FcRn binding**. A geometric mean with 95% confidence intervals is shown. (E) CL in human, (F) Q in human, (G) Vc in human, (H) Vp in human.

Source: Drug Metabolism and Pharmacokinetics 32 (2017) 208e217

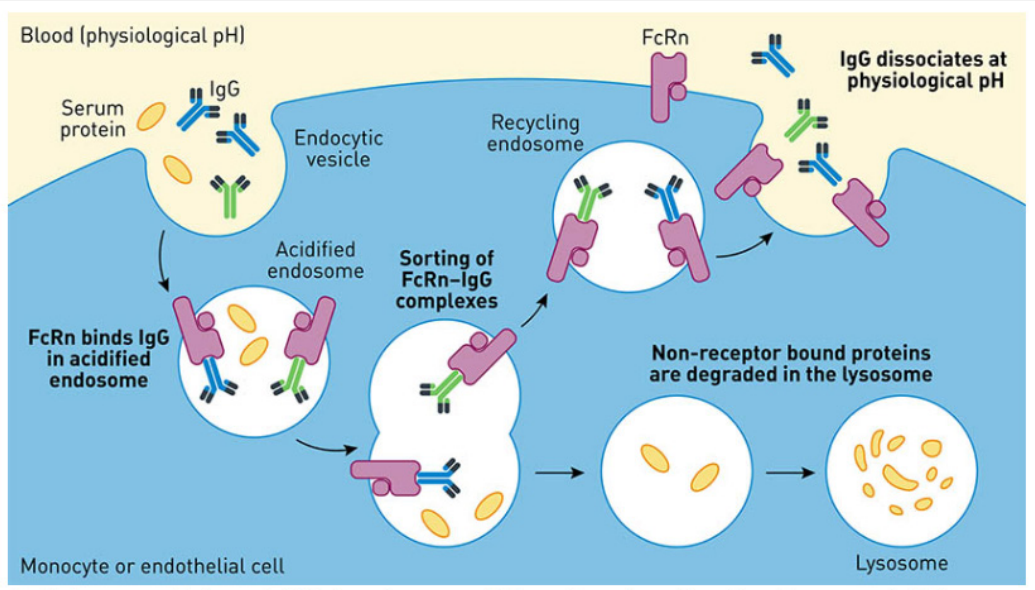


Fig 2. IgGs experience high serum half-life due to the protective FcRn recycling pathway. Adapted from Roopenian et al., 2007.

https://www.genengnews.com/sponsored/quick-facts-to-improve-antibody-half-life-measurements/

Elimination:

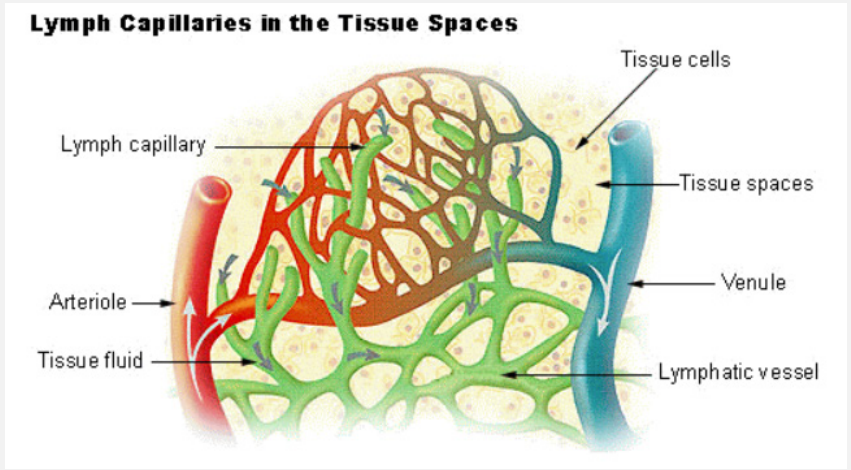
- Plasma half-life of mAbs is primarily regulated by protective binding with FcRn

There are 2 proposed mechanisms on how FcRn can impact mAb absorption:

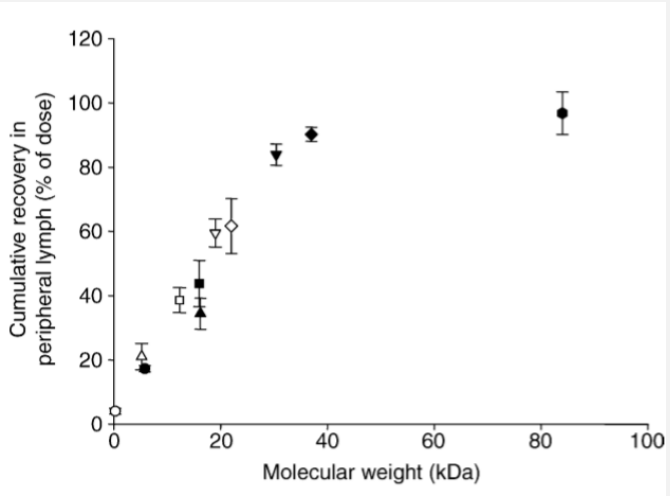
- FcRn-mediated **protection from degradation** at the injection site and
- FcRn-mediated **transcytosis from the interstitial space directly into the blood**

Absorption from SC injection site

- Subcutaneous tissue anatomy
  - Adipocytes grouped in lobules
  - Extracellular matrix (ECM):
    - Connective tissue: collagen & elastin fibers, GAGs (hyaluronic acid)
  - Vasculature: blood and lymphatic capillaries
- Absorption
  - In sheep lymphatics start dominating subcutaneous drug absorption from MW of around 19kDa
  - In rats FcRn binding shown to contribute to direct absorption into blood for rituximab



https://commons.wikimedia.org/wiki/File:Illu_lymph_capillary.png

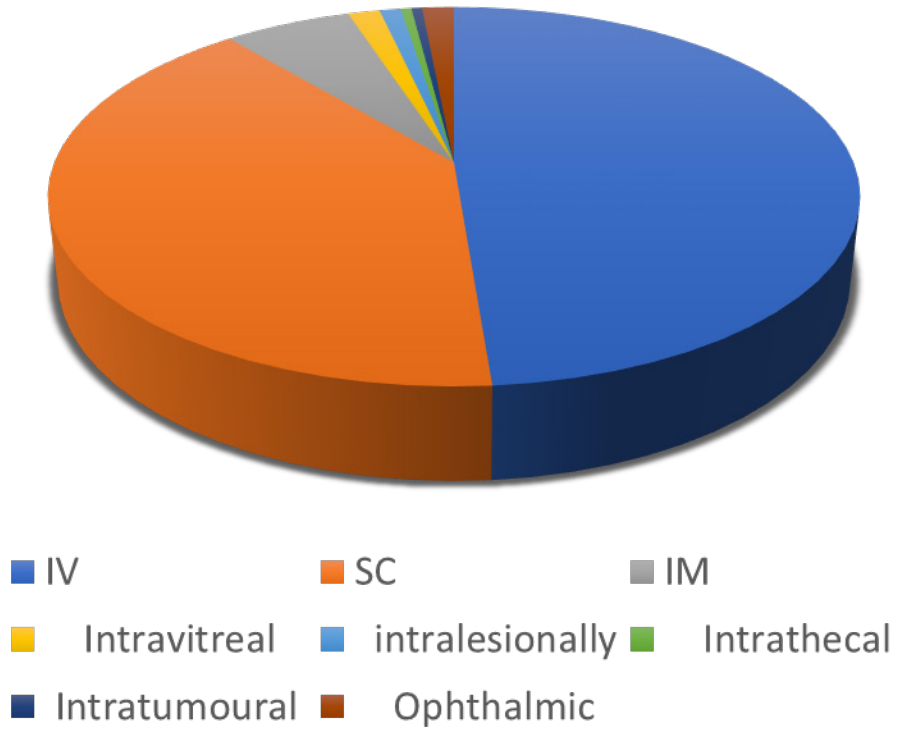


Drug Discovery Today: Technologies Volume 2, Issue 1, Spring 2005, Pages 89-96;
Drug Metab Dispos 41:248–255, January 2013

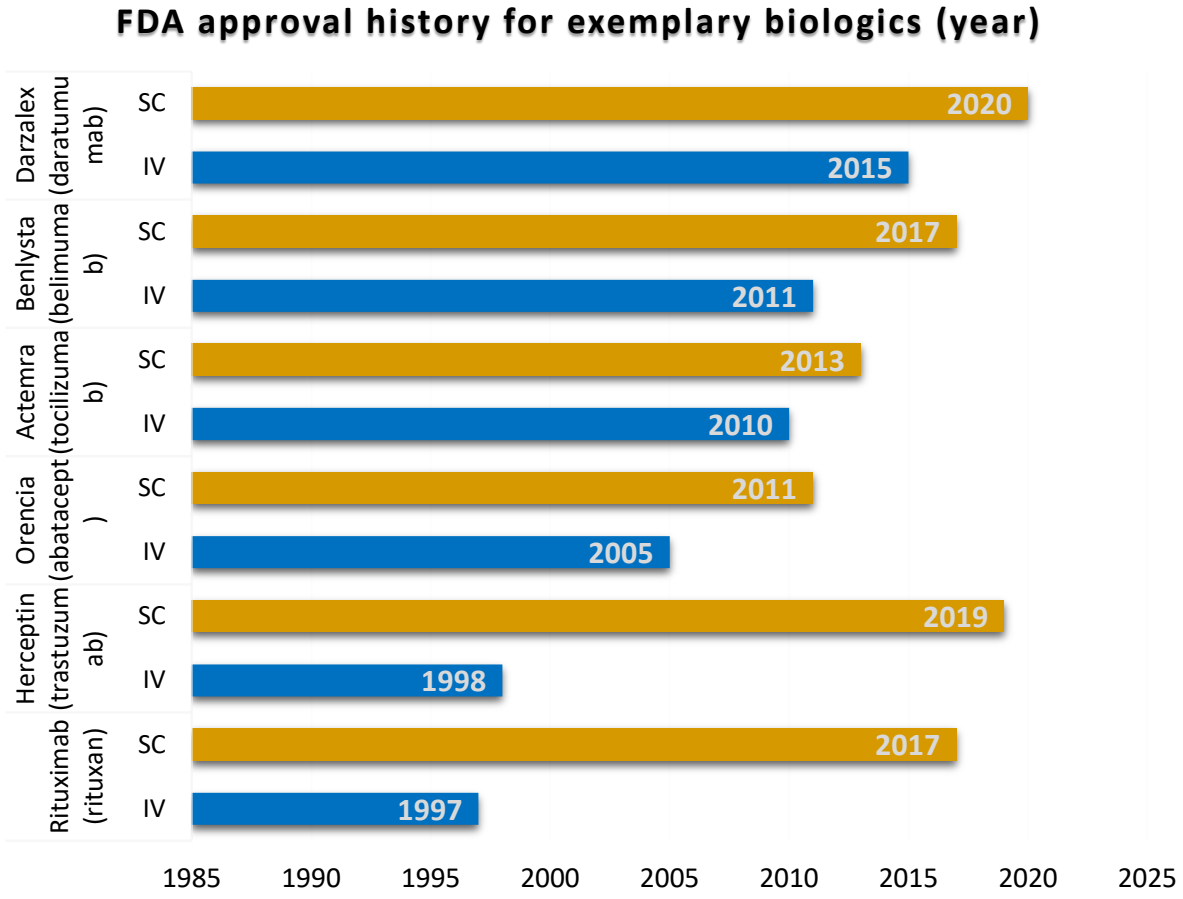
Drug Discovery Today: Technologies Volume 2, Issue 1, Spring 2005, Pages 89-96
https://doi.org/10.1016/j.ddtec.2005.05.006

IV to SC switch

IV and SC drug products



Intravenous administration is the conventional dosing approach. It provides the highest dose range.

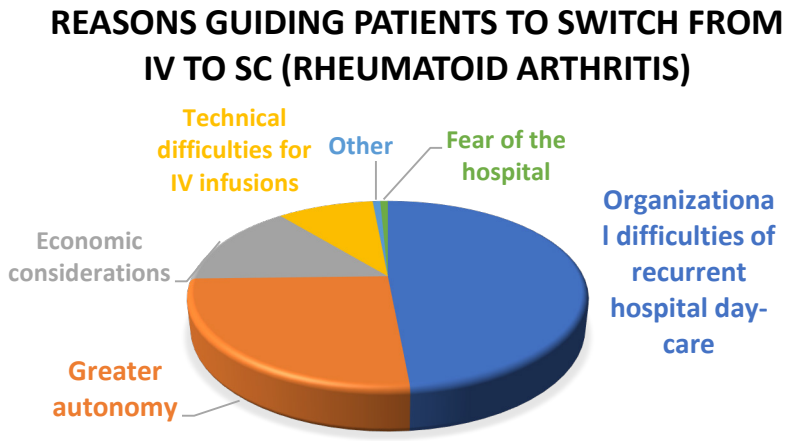


Exemplary biologic drug products for which IV formulation was approved first followed by a subcutaneous counterpart

Subcutaneous vs intravenous route

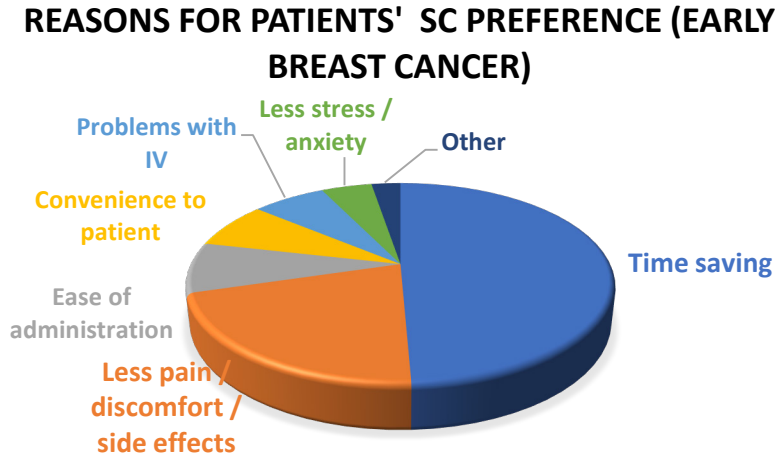
- SC route benefits
  - Greater patient convenience & adherence to the treatment
  - Less-complicated SC dosing procedure. Can be executed by a healthcare professional in an ambulatory setting or self-administered by a patient. IV administration requires preparation and infusion by a medical personnel using an aseptic technique
  - Decreased invasiveness of SC injections & lowered risk of systemic infections
  - Optimized use of resources & cost effectiveness for the healthcare system
  - Possibility of simplified dosing regimens: mpk-based or BSA-based IV dosing vs fixed dose for SC. Fixed dosing contributes to therapeutic safety and can simplify therapy not only for the patients but also for the medical personnel
- SC route challenges
  - Limitations to painless administration of larger fluid volumes
  - Incomplete SC bioavailability
  - Potential adverse events at the injection site

Patient preference surveys



Modified Fig 2 from Clin Rheumatol (2017) 36:1395–1400

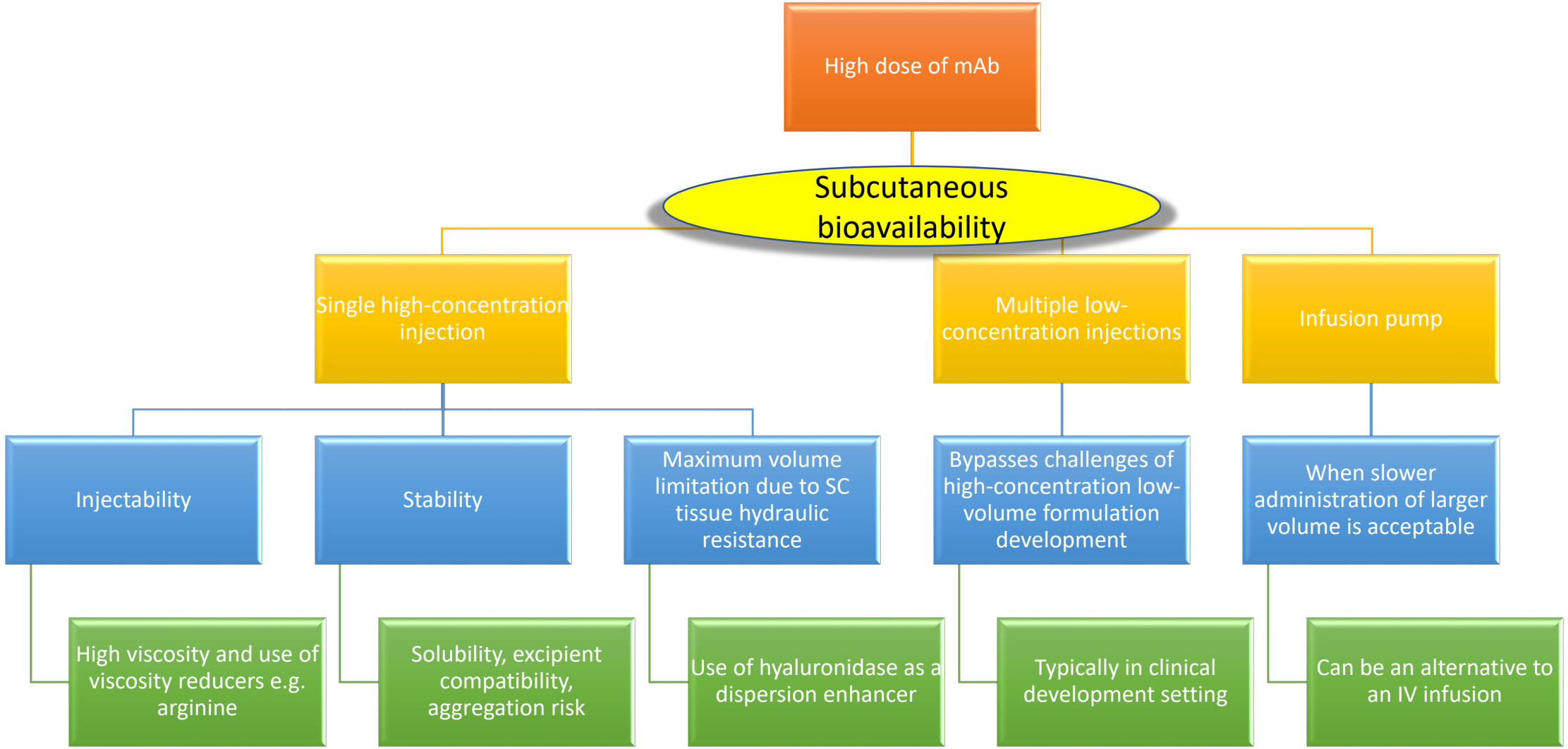
- Based on a prospective questionnaire from n=201 patients with rheumatoid arthritis patients treated with abatacept or tocilizumab
- "**Overall, 45.8% of the patients chose to keep the IV route** of administration (...) Patients reject the SC switch from the IV route of tocilizumab and abatacept mainly because of fears about the unknown SC route, while those who accept it find it more convenient."



Based on Table 2 from Annals of Oncology 25: 1979–1987, 2014

- Assessed by patient interviews after each patients received treatments via IV and SC routes, population N=488 patients
- Overall, **9.6% of patients preferred IV route**, 88.9% preferred SC, and 1.5% had no preference

High dose mAb: SC formulation development challenges



Typical characteristics of a subcutaneous formulation

Analysis based on a database comprised of 36 FDA-approved mAb and fusion protein SC drug products

- Type of formulation: 77% solutions vs 23% lyophilized powder
- Administration device:
  - prefilled syringe most common (63%)
  - 18% of drug products have both prefilled syringe and autoinjector
- API concentration:
  - Median 120mg/mL
  - Maximum 200mg/mL
  - Highest Viscosity = 90 cP [Xolair]
- Excipients:
  - Most common buffer: Histidine (52%)
  - Most common surfactant: PS80 (57%)
  - Most common tonicity modifier: Sucrose (52%)
  - pH Range: 4.7 to 7.4
- Dosing Volume
  - Maximum with injection/vial = 2mL [Takhzyro and Arcalyst]
  - Maximum with PFS = 1.5mL [Ajovy]
  - Maximum with infuser = 3.5 mL [Repatha]
  - Maximum with Hyaluronidase = 15 mL [Darzalex faspro]

Source: Merck internal analysis

Noninferiority trial – case of Darzalex (daratumumab)

- The primary hypotheses was that the **Overall Response Rate** and **C_{trough} for daratumumab** SC 1800mg are not inferior to the Overall Response Rate and C_{trough} for daratumumab IV 16mpk (mg/kg) in multiple myeloma patients which were previously treated
- Ph3 trial
- Population: patients with relapsed or refractory Multiple Myeloma, n=522
- Treatment groups:
  - IV Participants received daratumumab intravenous infusion (Dara IV) 16 mpk once weekly in Cycle 1 and 2, every 2 weeks in Cycle 3 to 6, every 4 weeks thereafter
  - SC Participants received daratumumab 1800mg flat dose subcutaneous injection (Dara SC) co-formulated with recombinant human hyaluronidase (rHuPH20) 2000 Unit per milliliter (U/mL), once weekly in Cycle 1 and 2, every 2 weeks in Cycle 3 to 6, every 4 weeks thereafter

Statistical analysis:

- The clinical non-inferiority for overall response of Dara SC relative to Dara IV was set using 60% retention of the ORR (i.e., a non-inferiority margin of 40%). The study needed to randomly assign (1:1) at least 480 patients to show noninferiority, with a power of 80% and a one-sided alpha of 0.025
- For maximum C_{trough}, the geometric means ratio (GMR) and the corresponding 90% CI of log-transformed C_{trough} were estimated. Non-inferiority of SC vs IV daratumumab was met if the lower limit of the 90% CI of the geometric means ratio exceeded 80%. Both co-primary endpoints needed to be met to show subcutaneous daratumumab noninferiority"

Source: 'Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial' Mateos, Maria-Victoria. *The Lancet Haematology* Volume: 7 Issue 5 (2020) and clinicaltrails.gov NCT03277105

Noninferiority trial – case of Darzalex (daratumumab)

	Subcutaneous group (N=263)		Intravenous group (N=259)		RR (95% CI)*	OR (95% CI)
	Proportion of patients or median	95% CI or IQR	Proportion of patients or median	95% CI or IQR		
Overall response†	108 (41%)	35·1–47·3	96 (37%)	31·2–43·3	1·11 (0·89–1·37)	1·19 (0·83–1·69)
Best overall response†						
Complete response or better	5 (2%)	0·6–4·4	7 (3%)	1·1–5·5	..	0·71 (0·22–2·27)
Stringent complete response	2 (1%)	0·1–2·7	2 (1%)	0·1–2·8	..	1·02 (0·14–7·31)
Complete response	3 (1%)	0·2–3·3	5 (2%)	0·6–4·4	..	0·59 (0·14–2·48)
Very good partial response or better	50 (19%)	14·5–24·3	44 (17%)	12·6–22·1	..	1·16 (0·73–1·85)
Very good partial response	45 (17%)	12·8–22·2	37 (14%)	10·3–19·1	..	1·25 (0·77–2·03)
Partial response	58 (22%)	17·2–27·6	52 (20%)	15·4–25·5	..	1·13 (0·73–1·74)
Minimal response	25 (10%)	6·2–13·7	28 (11%)	7·3–15·2	..	0·87 (0·49–1·53)
Stable disease	102 (39%)	32·9–45·0	94 (36%)	30·4–42·5	..	1·11 (0·78–1·58)
Progressive disease	19 (7%)	4·4–11·1	27 (10%)	7·0–14·8	..	0·66 (0·35–1·22)
Not evaluable	9 (3%)	1·6–6·4	14 (5%)	3·0–8·9	..	0·63 (0·27–1·49)
Median time to first response, months‡	1·0	1·0–1·9	1·0	1·0–1·9	..	..
Median time to very good partial response or better, months§	1·9	1·0–3·1	1·1	1·0–3·8	..	..

OR=odds ratio. RR=relative risk. *Farrington-Manning estimates of RR of subcutaneous over intravenous daratumumab. †Clopper-Pearson exact CIs for response rates. ‡n=108 for the subcutaneous group, n=96 for the intravenous group. §n=50 for the subcutaneous group, n=44 for the intravenous group.

Table 2: **Best response according to International Myeloma Working Group criteria**

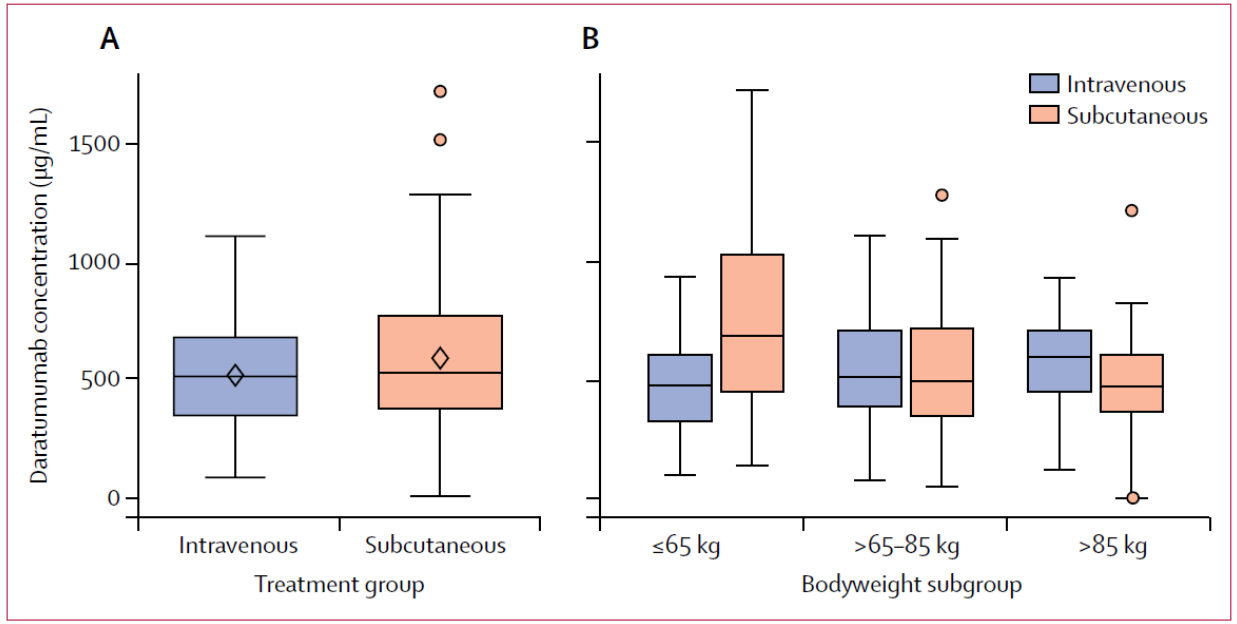


Figure 2: **Daratumumab trough concentration before cycle 3, day 1 dosing**
(A) Overall population. (B) Bodyweight subgroups. The boxes represent the 25th, 50th, and 75th percentile, and the whiskers represent the furthest values from the median that did not exceed 1·5 × IQR. Data above or below the respective whisker ends are considered outliers.

Overall responses were seen in 108 (41%) in the SC (95% CI 35.1–47.3) and in 96 (37%) in the IV group (31.2–43.3) with **relative risk 1.11, 95% CI 0.89–1.37** meeting the non-inferiority criterion

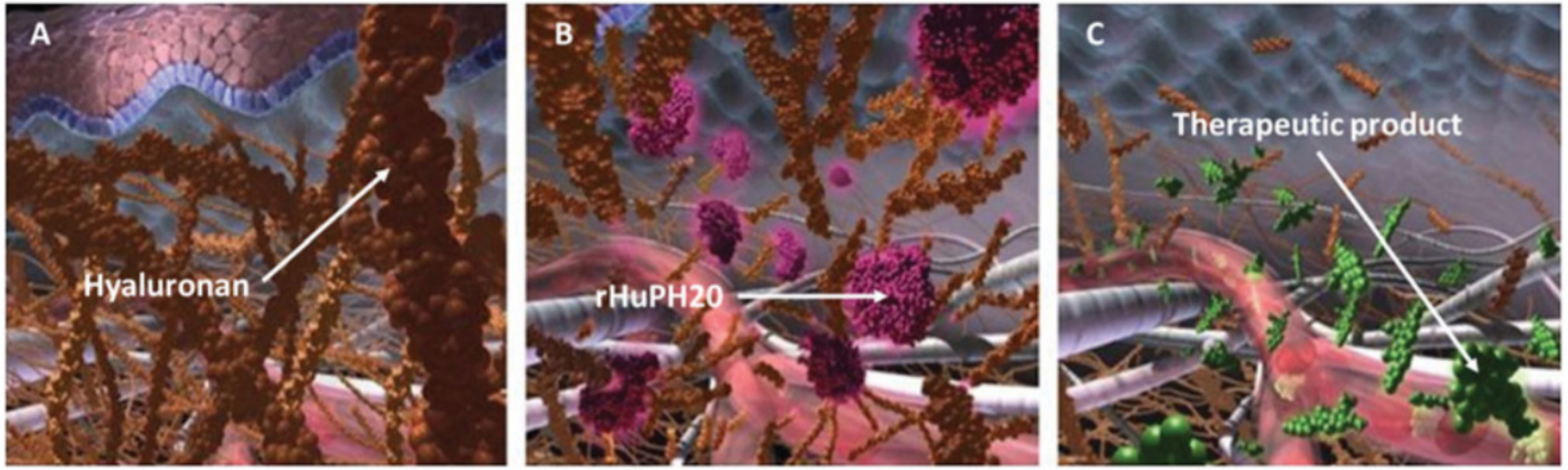
The GMR of Ctrough for the SC group vs IV group was 107.93% (90% CI 95.74–121.67) meeting the non-inferiority criterion

Source: 'Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial' Mateos, Maria-Victoria. *The Lancet Haematology* Volume: 7 Issue 5 (2020)

"Subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had an improved safety profile in patients with relapsed or refractory multiple myeloma"

Hyaluronidase as SC injection dispersion enhancer

Background



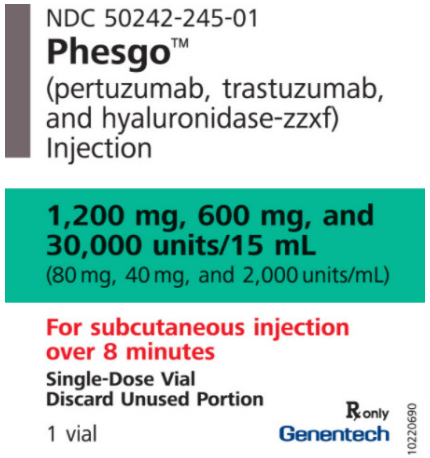
Source: Figure 1 from DRUG DELIVERY 2019, VOL. 26, NO. 1, 98–106

- Hyaluronic acid (HA) is a naturally occurring, gel-forming, biodegradable polymer. As a component of extracellular matrix (ECM) it imparts visco-elastic properties to tissues
- HA also provides hydraulic resistance to bulk fluid low thus limiting maximum volume that can be injected subcutaneously
- Pre- or co-administration of hyaluronidase (rHuPH20) with the drug of interest enzymatically cleaves HA polymer in the SC tissue enabling injections of larger volumes and facilitate spreading of the bolus. Structural elements of ECM (collagen or elastin) are not affected
- The impacted tissue regains homeostasis within 1-2 days due to natural fast turnover of HA

Mode of use

- **2-step sequential administration**
  - First hyaluronidase
  - Second therapeutic agent of interest
  - E.g. HyQvia label:
  - “Infuse the two components of HYQVIA sequentially, beginning with the Recombinant Human Hyaluronidase. Initiate the infusion of the full dose of the Immune Globulin Infusion 10% (Human) through the same subcutaneous needle set within approximately 10 minutes of the Recombinant Human Hyaluronidase infusion”

- **Simultaneous administration**
  - Co-formulation of therapeutic agent & hyaluronidase
  - E.g. Phesgo label:
  - “Administer subcutaneously over approximately 8 minutes”

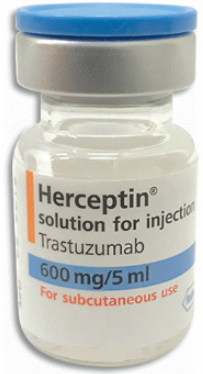


Enabling high volume SC mAb products

SC injection volume without hyaluronidase:

- Maximum with needle & syringe 2mL [Takhzyro and Arcalyst]
- Maximum with PFS = 1.5mL [Ajovy]

SC injection volume with hyaluronidase:



5mL

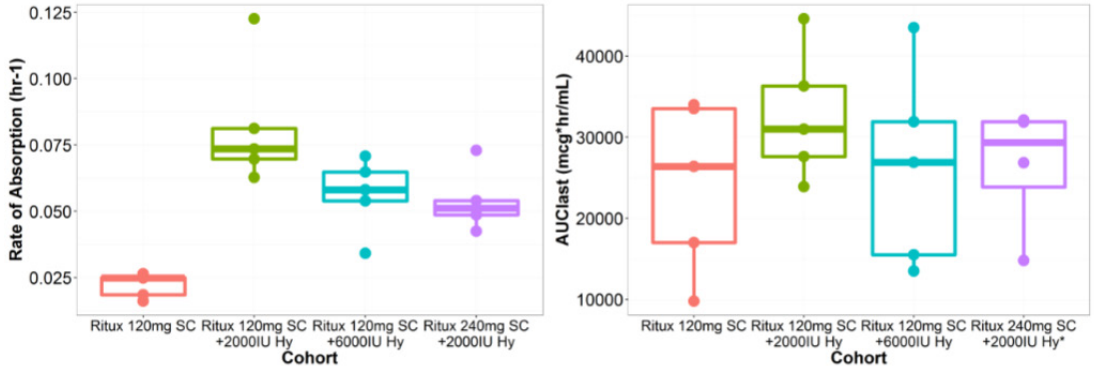
15mL

13.4mL

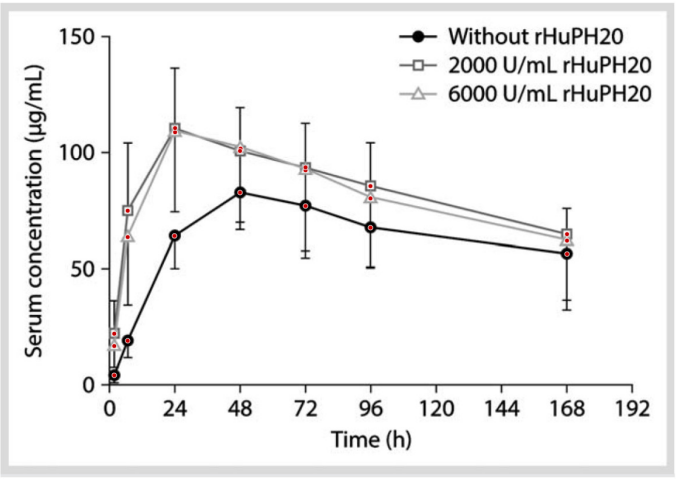
Rituximab case - preclinical PK in Gottingen minipigs

- A proof-of-concept study in Gottingen minipigs
- Inclusion of hyaluronidase at 2000IU/mL or 6000IU/mL increased the rate of absorption of rituximab around 3-fold and manifesting itself in a shortened T_{max}
- Minimal or no impact on the extent of absorption (BA 52% without hyaluronidase)

Figure 1: Absorption rate and exposure for rituximab SC in minipigs with and without hyaluronidase



FDA's clinical pharmacology and biopharmaceutics review(s) BLA# 761064



2014 Nov;64(11):569-75. doi: 10.1055/s-0033-1363993.

Rituximab case - clinical PK & comparison

- Dosage form:
  - Rituximab at 120mg/mL + hyaluronidase at 2000IU/mL
  - SC injection over 5 minutes
  - 2 different strengths: dose 1400mg (11.7 mL) and 1600mg (13.3 mL)
- Dosing regimen fixed (as opposed to IV regimen normalized per body surface area)
- There are no reported clinical PK data comparing SC formulations of Rituximab with and without hyaluronidase

Table 2: Pharmacokinetic Parameters of Rituximab SC[a]

	FL	CLL
Absorption		
Estimated Absolute Bioavailability[b]	0.646 (NA)	0.633 (21)
Distribution		
Volume of Central compartment[c] (L)	4.06 (26)[d]	4.80 (18)
Apparent Volume of Distribution at steady state[c] (L)	8.09 (19)[d]	8.52 (13)
Elimination		
Terminal Half-life (hours)	34.1 (27)	32 (24)
Effective Clearance (L/day)	0.18 (34)	0.204 (31)

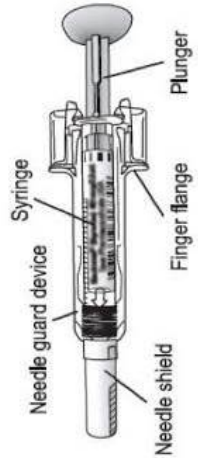
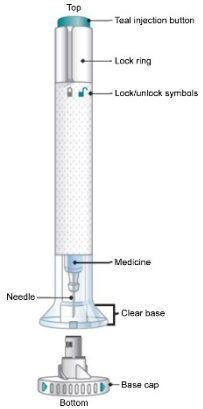
[a] Parameters represented as geometric mean (%CV) unless otherwise specified;
[b] Compared to rituximab IV
[c] Volume of central compartment and peripheral compartment
[d] NA=Not available

Rituxan Hycela FDA label

Rituximab Dose in minipigs	Formulation / hyaluronidase conc.	ka (day^{-1})	T_{max} (hr)	AUC Ratio	C_{max} Ratio
120	No rHuPH20	**0.79**	48	**Ref (F = 52%)**	Ref
120	2000 U/mL rHuPH20	**3.05**	24	**1.08**	1.34
120	6000 U/mL rHuPH20	**2.35**	24	**1.00**	1.31
Rituximab Dose in humans	**Formulation / hyaluronidase conc.**			**F**	
1400-1600 mg	120 mg/mL RTX, 2000 U/mL Hyaluronidase	**0.34 - 0.37**	72	**F = 63-65%**	

Formulation bridging in subcutaneous products

mAb drug product will have multiple product delivery format in development and might require clinical bridging

	Early phase (I &II)	Late phase (III)	Commercialization
Formulation	Solution/frozen/Lyo Platform composition Low concentration	solution Improved formulation High concentration	
DS/DP processes	Platform processes	Yield/titer/cost etc.	Robustness/cost etc.
Devices	 Vial and syringe	 Prefilled syringe	 Prefilled syringe	 Autoinjector/Pen injector

- early phase have limited product info (dose, dosing regiment, weight based, market considerations)
- Commercial devices are introduced in late-stage trial or during registration.
- Anal comparability to assess impact on molecule, potentially need clinical bridging if factors can affect SC absorption

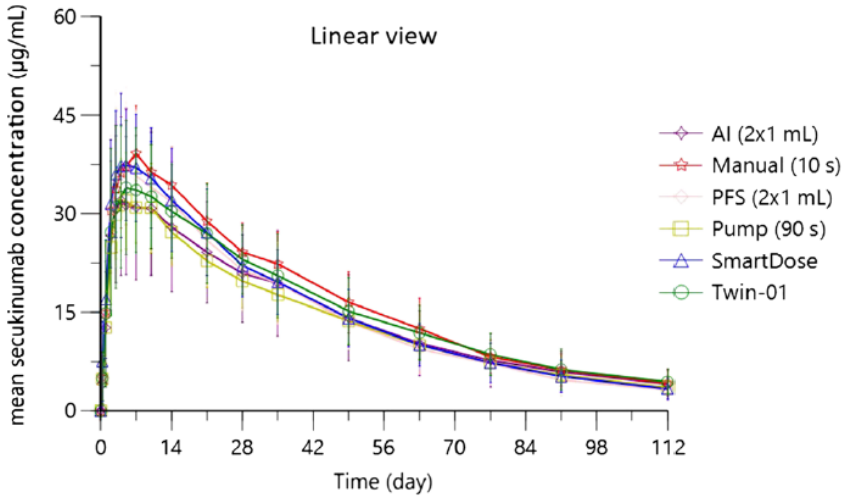
Rate of injection/infusion in SC tissue: secukinumab case

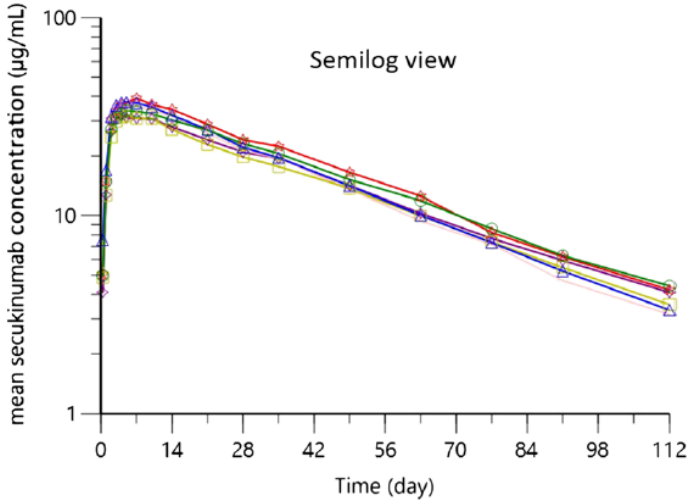
- **Potential concern**: SC injection rate or injection volume can create local hydrostatic pressure differences and affect absorption

TABLE 1 2-mL devices used for subcutaneous administration of secukinumab

	Needle length/estimated depth of injection	Injection time	Short label [a]	Ph 1 study	Ph 3 study
Auto-injector twice, 2 × 1 mL	12 mm/8 mm	10 s	AI (2 × 1 mL)	X	
Twin-01, 2 × 1 mL	12 mm/8 mm	10 s	Twin-01	X	
Syringe pump, 2 mL in 90 s)	6 mm	90 s	Pump (90 s)	X	
2-mL SmartDose, 2 mL in 5 min	5 mm	5 min	SmartDose	X	
Manual injection, 2 mL in 10 s	12 mm/8 mm	10 s	Manual (10 s)	X	
One PFS twice, 2 × 1 mL	12 mm/8 mm	10 s	PFS (2 × 1 mL)	X	X
One 2-mL PFS, 2 mL	12 mm/8 mm	10 s	PFS (2 mL)		X

[a]Where useful, the above nomenclature is used for the different delivery systems.



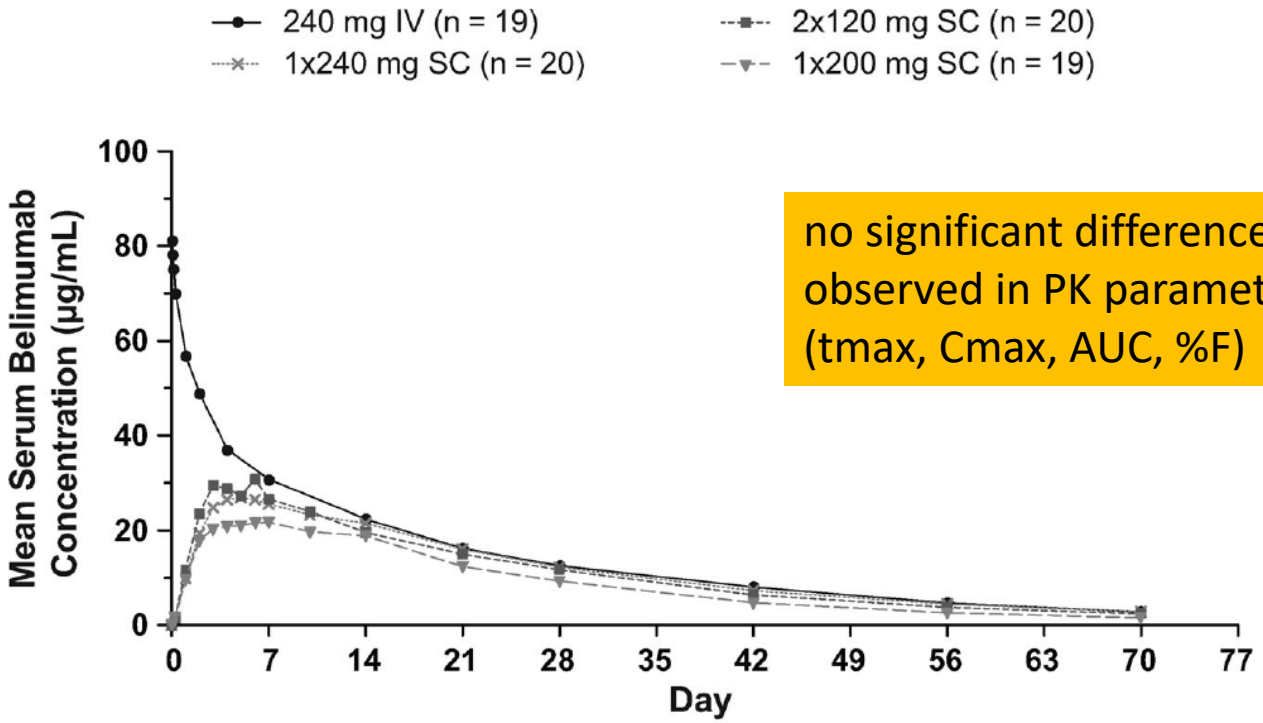


Injection time varying between 5 min and 10 s (for 2 mL volume), resulting in a variation of injection speed from 0.2 to 6.7 mL/min, did not affect the systemic PK profile of secuknumab after SC administration.

Bruin et al, Br J Clin Pharmacol. 2020;86:338–351

Volume of injection/infusion in SC tissue

Belimumab:
volume of injection 1x 1.2 mL vs 2 x 0.6 mL



no significant differences observed in PK parameters (tmax, Cmax, AUC, %F)

Clinical Pharmacology in Drug Development, 2013, 2(4) 349–357

Secukinumab:
Volume of injection 1x 2mL vs 2x 1mL

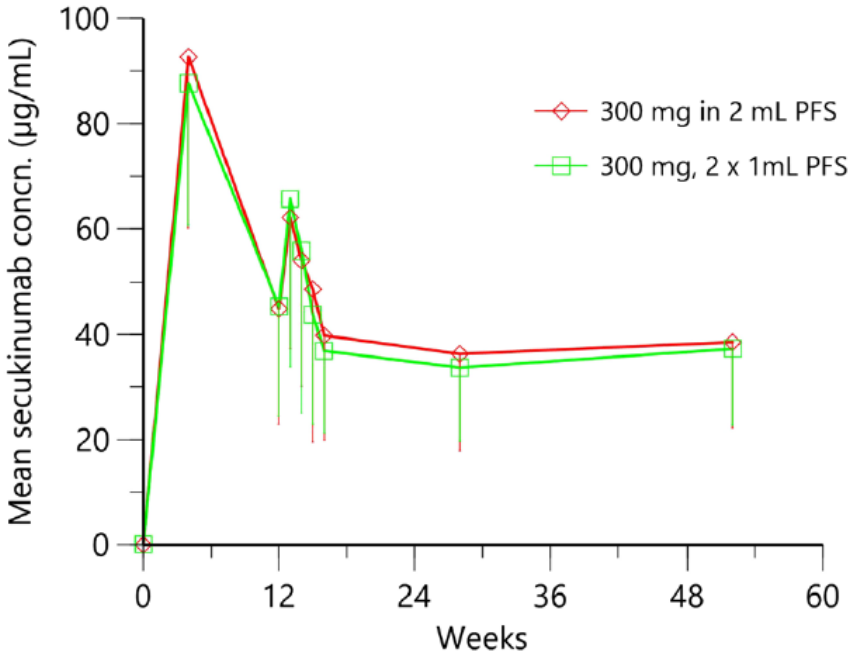


FIGURE 3 Time–mean serum concentration pharmacokinetic trajectories with 2 × 1-mL and 2-mL prefilled syringe (PFS) injection devices in psoriasis patients

Bruin, Br J Clin Pharmacol. 2020;86:338–351

Formulation composition change: emicizumab concentration

Potential concerns: Formulation concentration (or viscosity etc.) can cause differences in tissue transport and affect absorption

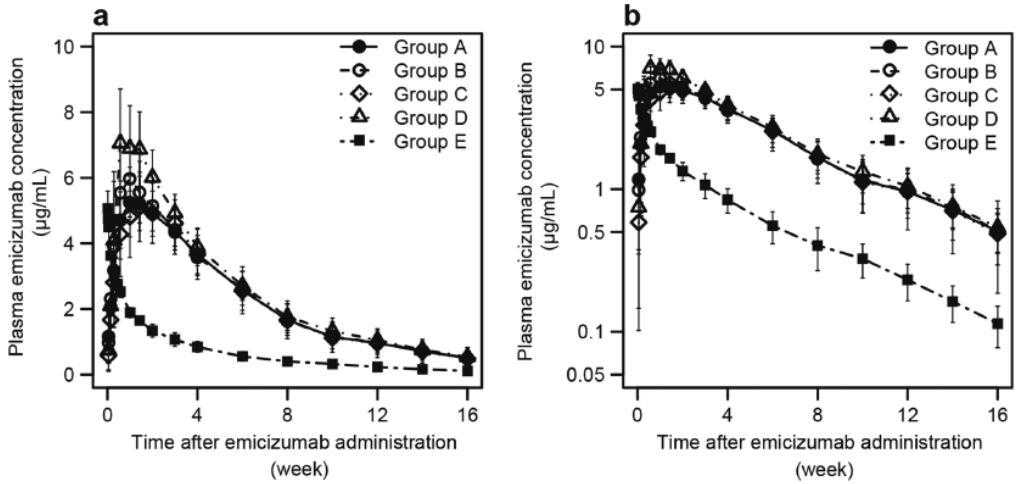


Figure 2. Mean (± SD) time courses of plasma emicizumab concentration following a single subcutaneous injection of 1 mg/kg with the old drug product into the abdomen (group A), a single subcutaneous injection of 1 mg/kg with the new drug product into the abdomen (group B), upper arm (group C), and thigh (group D), and a single intravenous infusion of 0.25 mg/kg with the new drug product (group E). Data below the quantification range were handled as missing in summary statistics calculation. Summary statistics were not calculated when measured values were below the quantification range in the majority of subjects for each group and time point. a, Linear plot. b, Semilogarithmic plot.

80 mg/mL DP 150 mg/mL DP

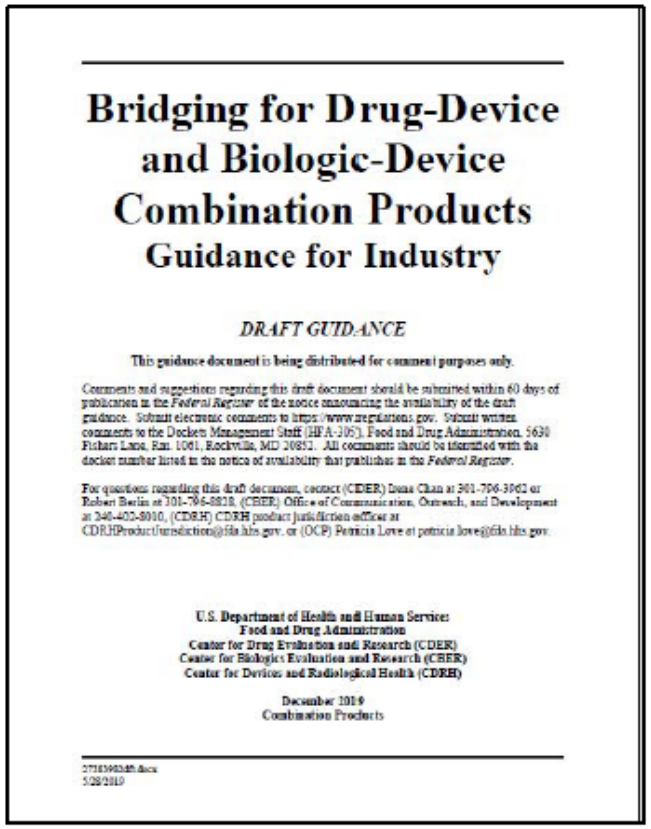
Table 2. Pharmacokinetic Parameters of Emicizumab Following a Sing

Parameter	A (SC)	B (SC)
N	12	12
C_{max} (μg/mL)	5.40 ± 0.907	6.26 ± 1.26
T_{max} (d)	6.97 (3.99-10.9)	6.97 (3.98-14.0)
AUC_{last} (d·μg/mL)	247 ± 56.8	253 ± 47.7
AUC_{inf} (d·μg/mL)	271 ± 76.2	274 ± 53.3
$t_{1/2}$ (d)	28.7 ± 7.43	28.0 ± 5.53
CL/F (mL/[d·kg])	3.98 ± 1.19	3.84 ± 1.05
CL (mL/[d·kg])	...	...
$V_{d,z}$ (mL/kg)	...	...
$V_{d,ss}$ (mL/kg)	...	...
F (%)	...	0.868[a] (0.795-0.948)

"Similar pharmacokinetic profiles were observed between the DPs, with geometric mean ratios of 1.199 (90% confidence interval [CI] 1.060-1.355) for the maximum plasma concentration and 1.083 (90% CI 0.920-1.275) for area under the plasma concentration-time curve extrapolated to infinity. "

Kotani Clinical Pharmacology in Drug Development 2019,8(6) 702–712

Clinical bridging for introducing drug/device and combination products for mAb



Bridging for Drug-Device and Biologic-Device Combination Products
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dana Chan at 301-796-3962 or Robert Berlin at 301-796-8828, (CBER) Office of Communication, Outreach, and Development at 240-402-8010, (CDRH) CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov, or (OCP) Patricia Love at patricia.love@fda.hhs.gov.

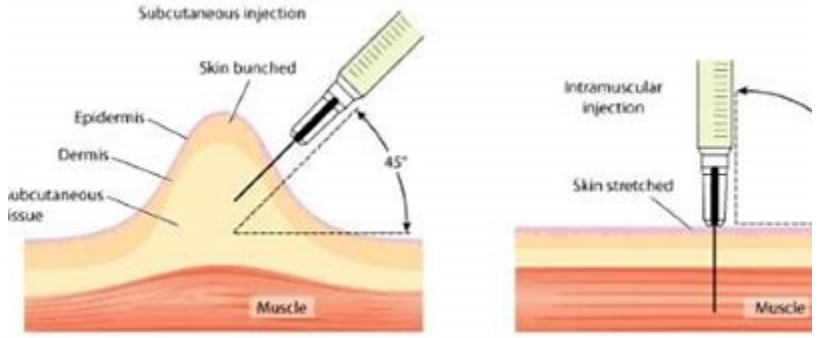
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2019
Combination Products

Published 2019

- Current guidance requires PK bridging study for drug/device combination (e.g., between PFS and autoinjector) due to the perceived difference in delivery method and potential product variation

	PFS	Autoinjector
Injection mode	Manually	Automatic (~10s)
Injection angle	45º	90º
Tissue plane	Pinched skin	Flat skin
Injection depth	12.5 mm needle/8mm	~8mm (4.5~10.5 mm)



- A recent review of BLA filing (up to 2018) suggests that maximum AI injection depth could affect the outcome on BE. However, results are for broad SC products and not mAb specific.

Table IV. Summary of Key Information for AI Injection Depth and PK Comparability Studies Presented by Three Categories of Maximum AI Injection Depth

Summary				Device		Pharmacokinetics (PK)	PK study			
Max. AI inj. depth (mm)	No. of BLA[b]	PK outcome	PK-non-BE (fraction)	AI inj. depth (range, mm)	Parameter[c]	Geometric mean ratio (90% CI)—AI/PFS	Study design	*N* per arm	% CV of C_{max} (observed)	Statistical power/ empirical
N/A	3									
< 8[a]	5	*N* = 5, PK-BE	0%							
8	2	PK-non-BE	50%	4.5–8.0	C_{max}	1.17 (0.90–1.53)	Crossover	23[d]	48	Empirical
		PK-BE		5.0–8.0	C_{max}	1.05 (0.94–1.18)	Parallel	38	33	Empirical
> 8	4	*N* = 3, PK-non-BE	75%	5.5–9.5	C_{max}	1.11 (0.96–1.27)	Parallel	70[e]	51	0.8
				6.0–10.0	C_{max}	1.10 (0.97–1.254)	Parallel	35[f]	51	Empirical
				5.5–10.5	$C_{trough,t1}$	1.25 (1.16–1.35)	Parallel	50[g]	N/A[g]	Empirical[g]
					$C_{trough,t2}$	1.38 (1.22–1.57)				
		PK-BE		5.5–10.5	C_{max}	1.01 (0.94–1.08)	Crossover	48[h]	N/A	0.9

Hu et al. Systematic Review of Device Parameters and Design of Studies Bridging Biologic-Device Combination Products Using Prefilled Syringes and Autoinjectors, AAPS J, 2020, 22: 52

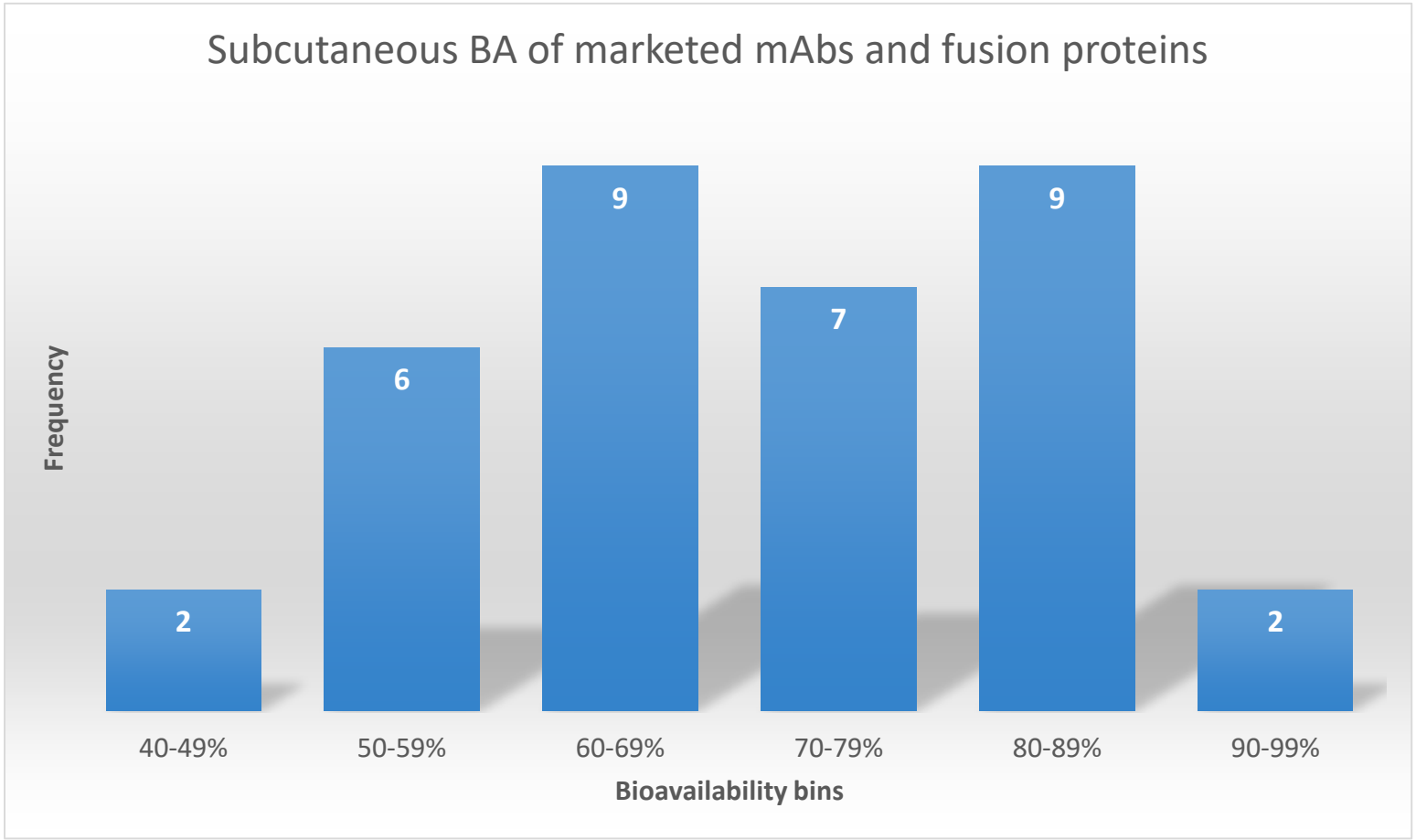
Survey of filed mAb products for their BE success rate using different containers/devices

Product	PK study	N of each arm	Outcome
Mepolizumab[1]	• PFS vs. autoinjector, vs. reconstituted lyo liquid	~80	statistically comparable PK. Met bioequivalence criteria
certolizumab pegol[2]	• PFS vs. Autoinjector	49	bioequivalent whether administered by AI or PFS
secukinumab[3]	• PFS vs. reconstituted lyo liquid in vial	70	Met bioequivalence criteria
Transtuzumab containing rHuPH20[4]	• Syringe (~3 min) • Proprietary SC infuser (patch pump)	~60	Met bioequivalence criteria
Canakinumab[5]	• PFS vs. reconstituted lyo liquid (different matrix as well)	~65	Met bioequivalence criteria
Belimumab[6]	• PFS vs. autoinjector	38	Met bioequivalence criteria
Golimumab[7]	• Liquid-in-vial vs. PFS, vs. autoinjector	~70	Met bioequivalence criteria
Benralizumab[8]	• PFS vs. autoinjector	90	Met bioequivalence criteria
Erenumab[9]	• Vial vs. PFS, vs. Autoinjector		Met bioequivalence criteria
Galcanezumab[10]	• PFS, vs. Autoinjector	80	Met bioequivalence criteria
Evolocumab[11]	• PFS vs. Autoinjector	48	Met bioequivalence criteria

1. Shabbir et a. Clinical Pharmacology in Drug Development, 2020, 9(3) 375–38
2. https://ard.bmj.com/content/75/Suppl_2/1003.1
3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125504Orig1s000ClinPharmR.pdf
4. Wynne, Cancer Chemother Pharmacol (2013) 72:1079–1087
5. Chioato, Clin Drug Investig (2013) 33:801–808
6. StruemperH, et al. *ClinPharmacolDrug Develop* (2016) 5:208-215.
7. Xu Z, et al., Clin Ther. 2015 Feb 1;37(2):427-38.
8. https://doi.org/10.1080/02770903.2019.1663428
9. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761077Orig1s000ClinPharmR.pdf
10. Stauffer, Patient Prefer Adherence. 2018; 12: 1785–1795.
11. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000ClinPharmR.pdf

Bioavailability for subcutaneous products and preclinical to clinical translation

Distribution of Clinical SC bioavailability for licensed mAbs and fusion proteins

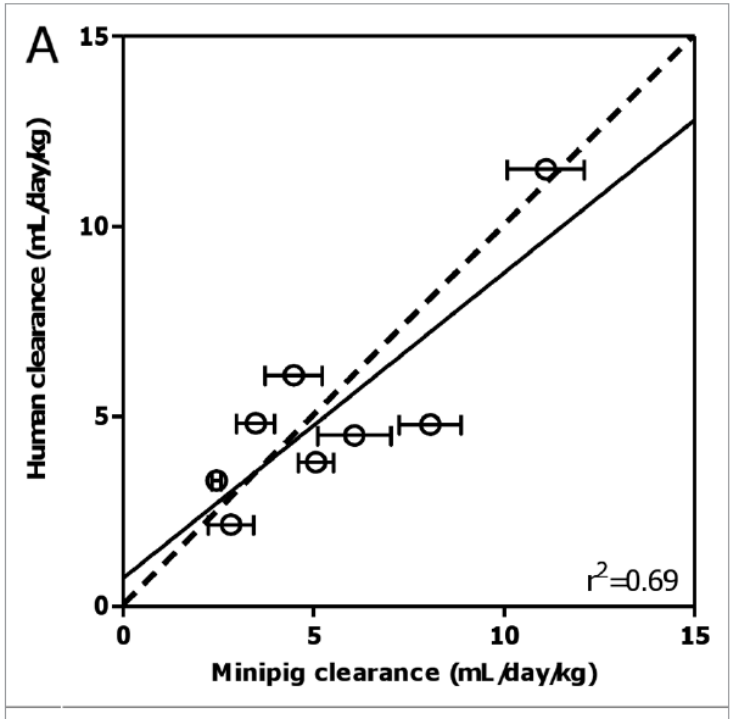


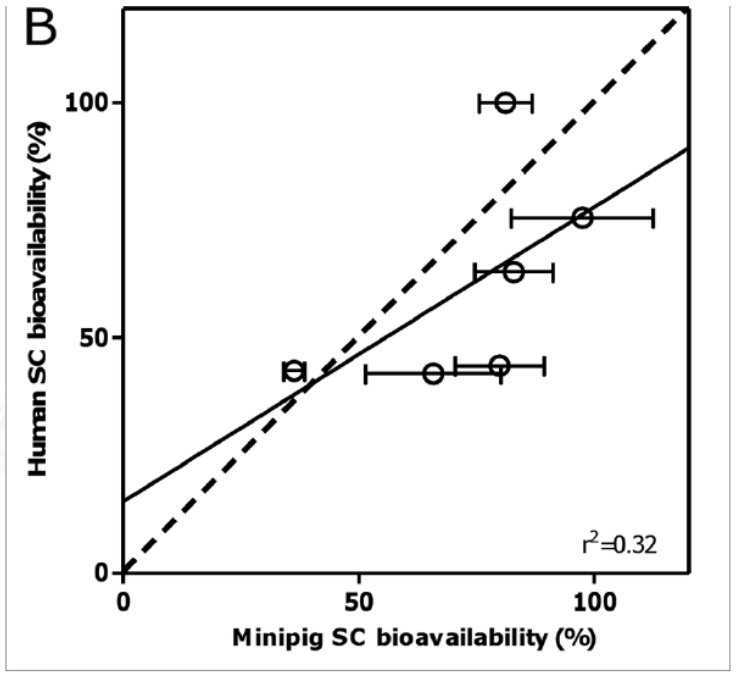
Source: Merck internal analysis

Preclinical to clinical translation: species differences for SC administration

SC properties compared to human	Mouse	Rat	Minipig	NHP	Human
Skin surface/injection volume	small	small	medium	medium	large
Tissue structure	less fibrous tissues and presence of panniculus carnosus		comparable skin anatomy to human	less abundant elastic fiber	-
Absorption rate	fast	fast	slow	slow	slowest
Lymph/capillaries	potentially higher lymph flow due to faster breathing and movement		less vascular and inverted lymph node		-
Metabolism/FcRn binding	-		FcRn binding similar to human	FcRn binding similar to human	-

Göttingen minipigs are previously tested for its prediction of human biopharmaceutics



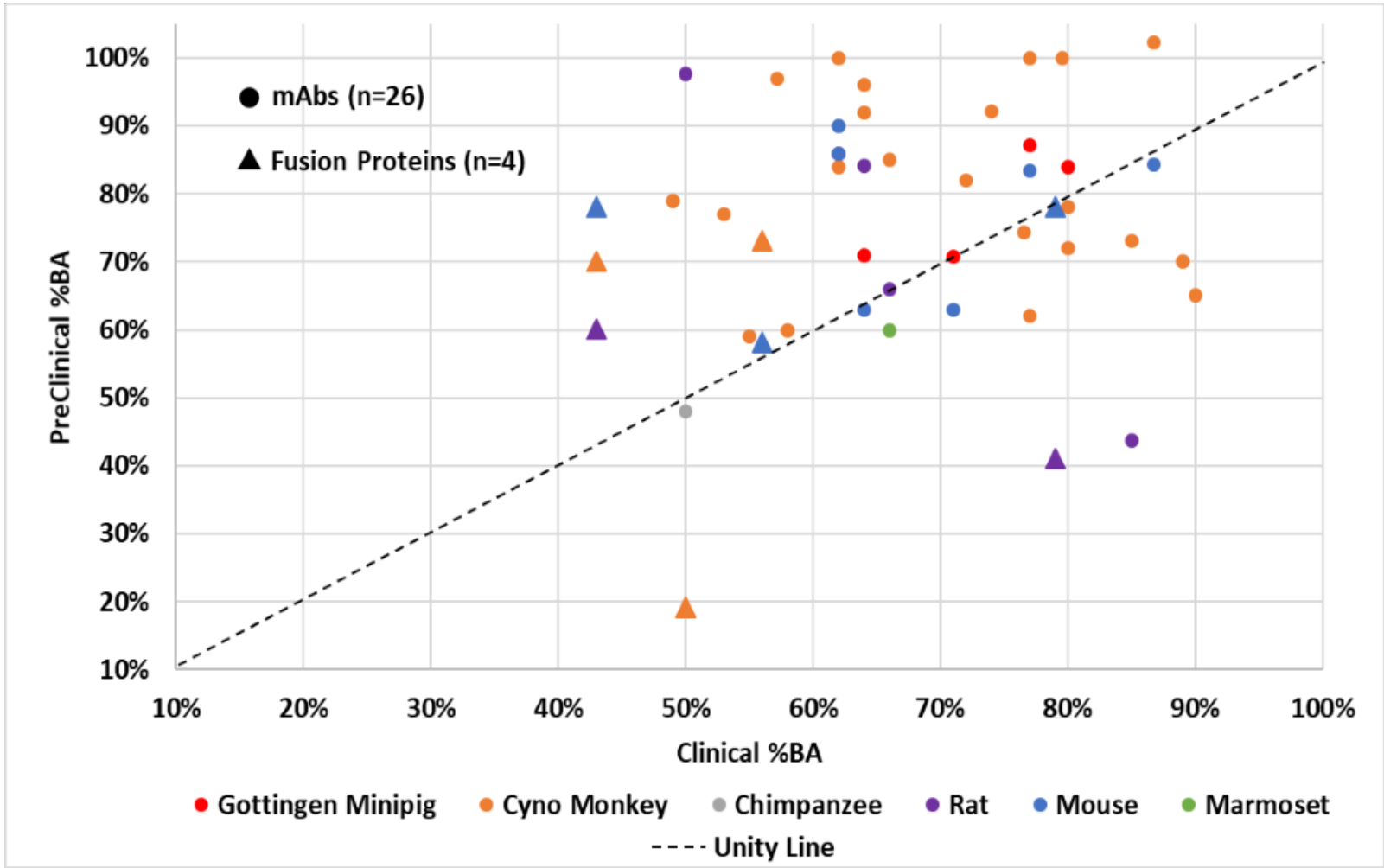


	Ka (1/day) in human	Ka (1/day) in minipig
mAb1	0.213	1.02
mAb2	0.251	0.316
mAb3	0.308	0.635
mAb4	0.321	1.61
mAb5	0.221	0.862

- Göttingen minipigs were able to predict human clearance,
- SC absorption rates were generally 2~5 fold higher compared with human
- however, SC bioavailability results showed poor correlation with those from human

Zhen et al., mAbs 2012, 4:2, 243-255

Preclinical to clinical translation: bioavailability aspect for licensed mAbs



Merck internal analysis of Preclinical to Clinical correlation of %BA for 26 mAbs and 4 fusion proteins.

Open questions

Focus areas of CRA Subcutaneous Drug Delivery & Development Consortium

- Explore the relationship **between large-volume and high-dose technology design attributes and the patient experience** in order continue to shift expectations and expand what is possible with novel SC technologies.
- **Clinical subcutaneous bioavailability of biologics** lacks reliable predictive methods (for commercial mAb/fusion protein products SC BA is in the 43-100% range). In-silico, in vitro, or preclinical models will be explored to inform molecule and product design of SC large molecule dosage forms.
- There is a lack of consistent **understanding about SC immunogenicity, relevant testing methodologies and corresponding quality attributes**. There is a gap in understanding of the nature of immune response after SC administration as a function of administered molecule and formulation, thus prohibiting SC developers from focusing on the most important considerations and product enhancements.
- **Patient preferences** are not clearly understood and prioritized by SC developers in order to identify key perceptions and differences regarding **optimal SC product design attributes**. Publicly available quantitative data is insufficient and opinions are ineffective and difficult to communicate.
- The **optimal time to initiate SC clinical trials during a product's lifecycle is unclear**. Some developers believe that SC trials should only be initiated when efficacy has been formally verified, while others believe that it is important to strategically begin SC trials as early as possible whenever it is an option.

Source: CRA Subcutaneous Drug Delivery & Development Consortium materials, edited

Acknowledgments

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- Maria Cueto, Yash Kapoor, Mikhail Murashov, Wei Zhu
- Filippos Kesisoglou, Sachin Mittal, Jason Cheung, Lei Zhu, Nicole Buist

Thank you!

Thank you for attending the webinar!

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PQRISecretariat@pqri.org

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