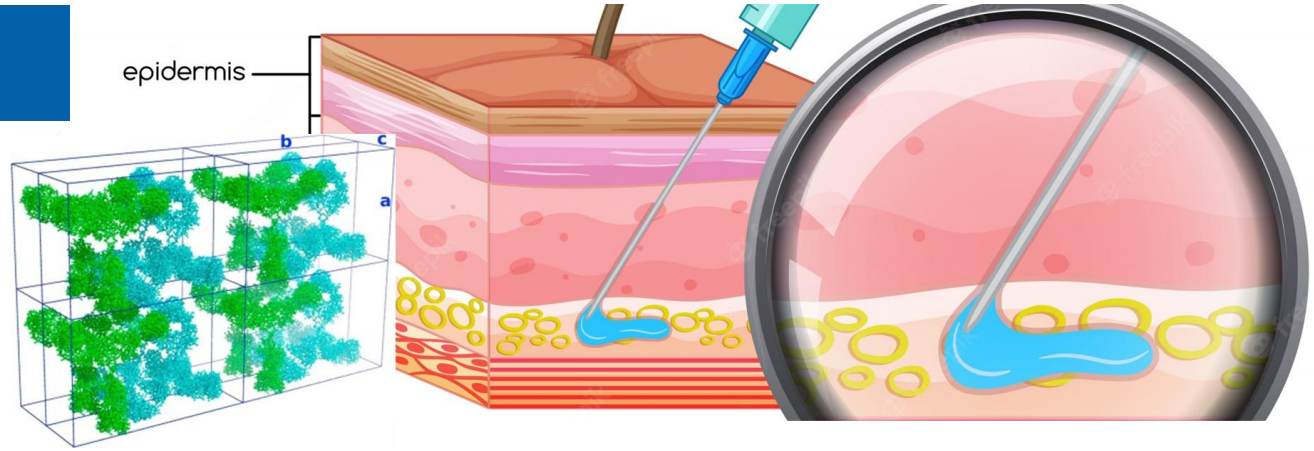
Technical Research & Development



SubQ Bioavailability Considerations

Manuel Sanchez-Felix

CASSS – CM&C Strategy Forum Europe 17th to 19th October 2022

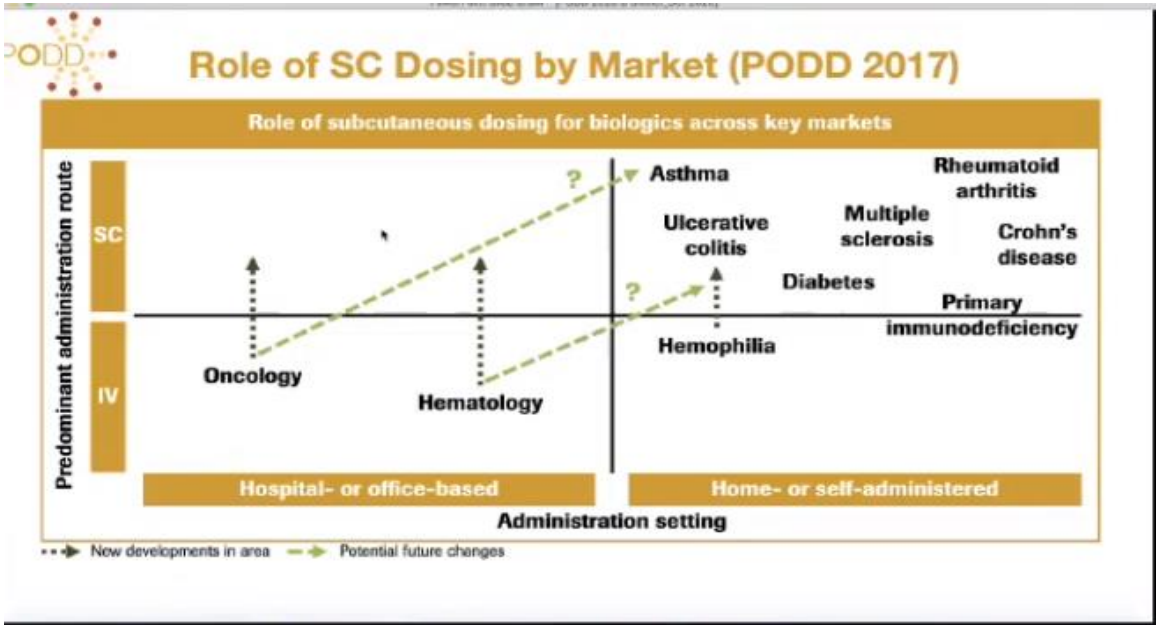
NOVARTIS | Reimagining Medicine

Introduction

- Highlight Trends from IV to SC products driven by patient needs
- Subcutaneous Drug Delivery & Development Consortium
- Subcutaneous Bioavailability Challenges
- Summary

Patient Centered Advantages & Trends of Subcutaneous

Trend in mAB from IV to SC

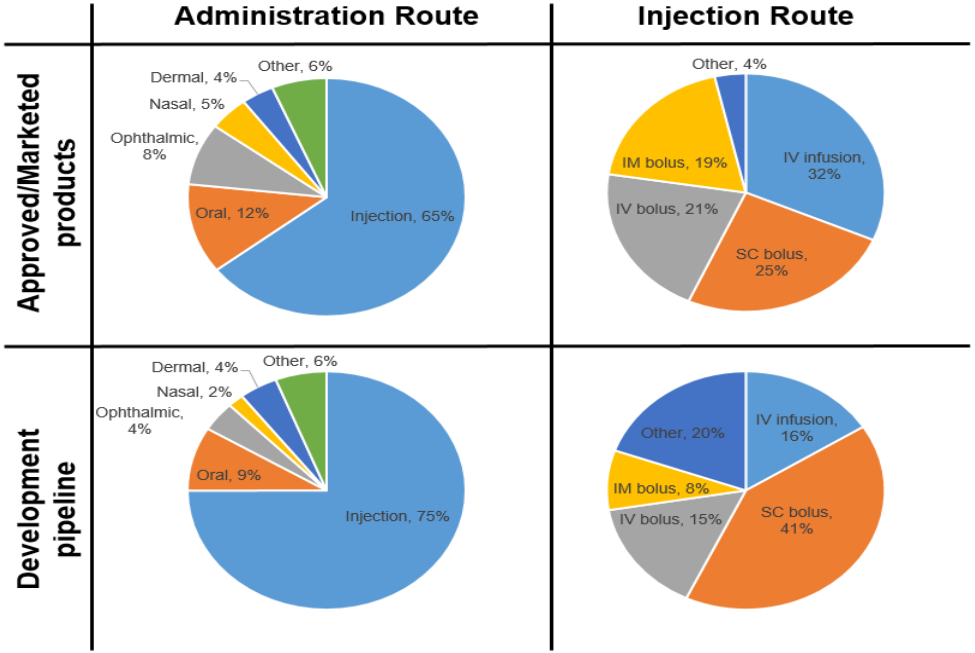


- Transition is being accelerated by COVID
- New classes of bispecific show higher efficacy SC

Beate Bittner, Roche, PODD Conference 2020

Patient Centered Advantages & Trends of Subcutaneous

Trend in Peptide from IV to SC in development pipeline



NOVARTIS | Reimagining Medicine

Ahil Ganesh, Carolyn Heusser, Sudhakar Garad & Manuel Sanchez-Felix, Patient-centric design for peptide delivery: Trends in routes of administration and advancement in drug delivery technologies, Medicine In Drug Discovery, 2021

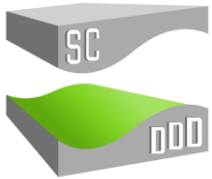
Subcutaneous Drug Delivery & Development Consortium

Vision

Our vision is to **transform patient care** and **improve patient outcomes** leading **fundamental advancements in subcutaneous drug development and delivery**

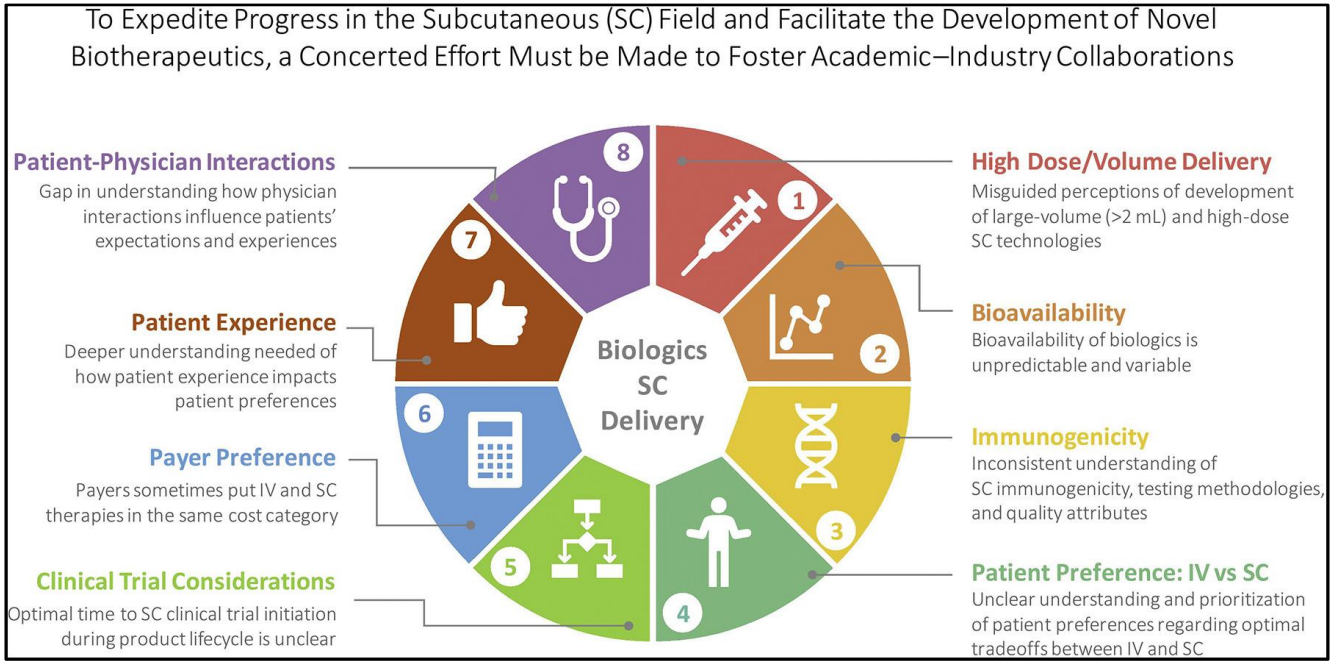
Mission

The mission of the Subcutaneous Drug Development & Delivery Consortium is to **collaboratively address the most pressing subcutaneous dosage and delivery issues and opportunities** in a **precompetitive manner**



NOVARTIS | Reimagining Medicine

Accelerating the development of novel technologies and tools for subcutaneous delivery of biotherapeutics subcutaneous

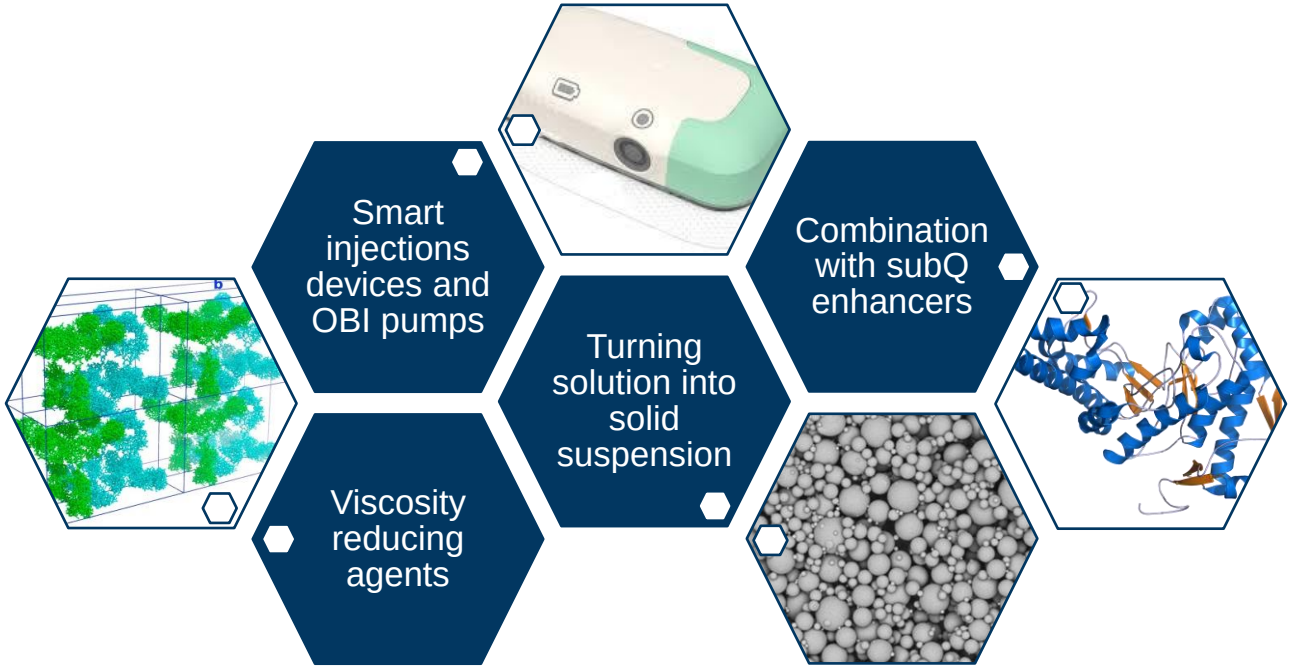


David S. Collins, Manuel Sanchez-Felix, Advait V. Badkar, Randall Mrsny, Journal of Controlled Release, 221, (2020), p. 475-482

Subcutaneous Drug Delivery & Development Consortium

The **top 6 problem statements** have been prioritized for 2020, with **6 sub-teams created around these statements** (the 2 patient statements have been combined into 1 sub-team).

Formulation & Device Options for SubQ Delivery – especially of higher doses



David S. Collins, Manuel Sanchez-Felix, Advait V. Badkar, Randall Mrsny, Journal of Controlled Release, 221, (2020), p. 475-482

Subcutaneous Bioavailability Challenges

ELSEVIER

Advanced Drug Delivery Reviews

Available online 27 May 2020

In Press, Corrected Proof

Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge

Manuel Sánchez-Félix [a], Matt Burke [b], Hunter H. Chen [c], Claire Patterson [d], Sachin Mittal [e]

Contents

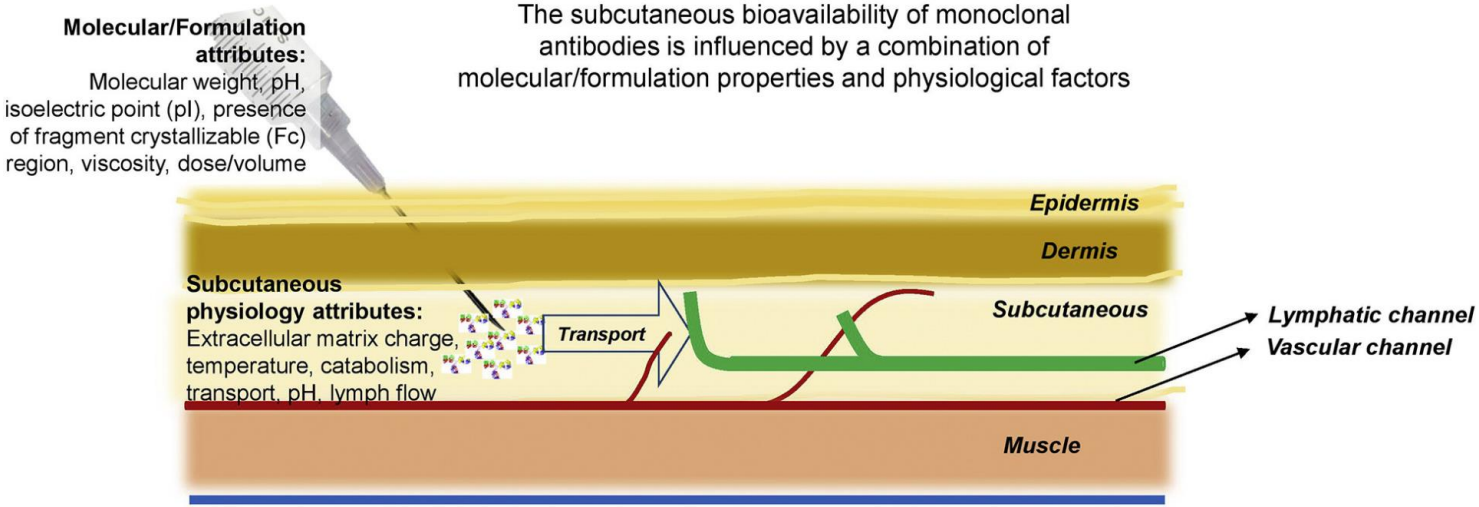
NOVARTIS | Reimagining Medicine

Subcutaneous Bioavailability Challenges

Commercialized Product Examples

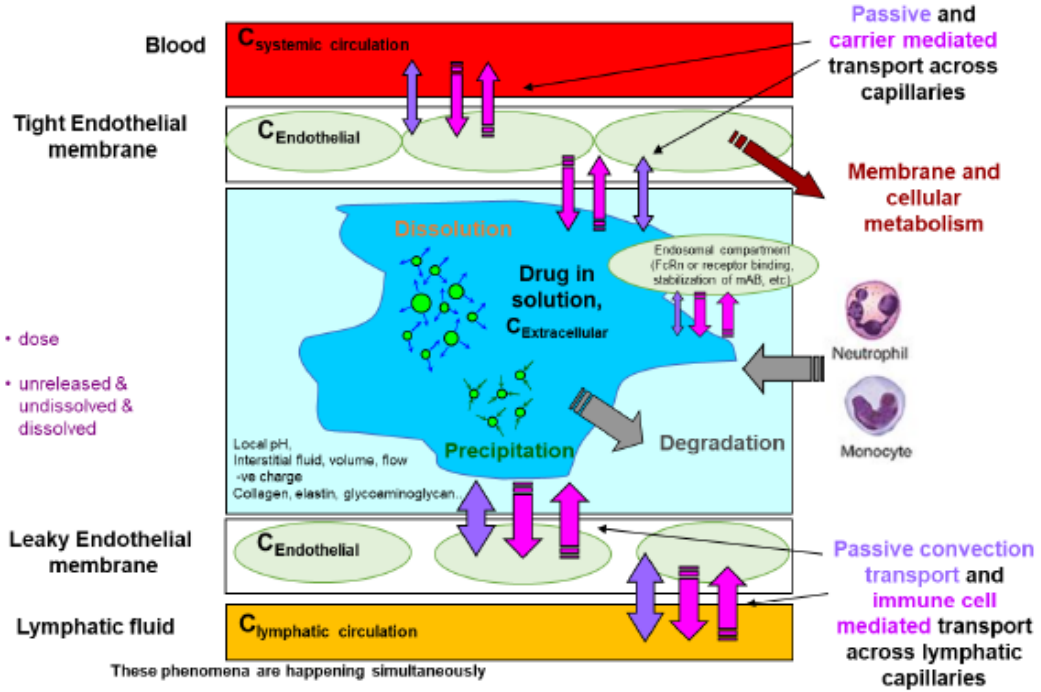
Molecule	Tradename	MW (kDa)	SC bioavailability
Adalimumab	Humira®	148	Human: 52–82% (64%) Monkey: 94–100% (96%)
Alirocumab	Praluent®	146	Human: 85% Monkey: 73–77% Rat: 44–97%
Canakinumab	Ilaris®	145	Human: 63–67% Monkey: 60%
Certolizumab pegol	Cimzia®	91	Human: 76–88% Rat: 24–34%
Etanercept	Enbrel®	150	Human: 76% Monkey: 73% Mice: 58%
Golimumab	Simponi®	150	Human: 53% Monkey: 77%
Omalizumab	Xolair®	149	Human: 53–71% (62%) Monkey: 64–104% (84%) Mice: 90%
Bevacizumab	Avastin®	149	Monkey: 98% Rat: 69% Mice: >100%
Rilonacept	Arcalyst®	251	Human: 43% Monkey: 70% Rat: 60% Mice: 78%
Rituximab	Mabthera®	145	Human: 71% Minipig: 71% Mice: 63%
Sarilumab	Kevzara®	150	Human: 80% Monkey: 78%
Trastuzumab	Herceptin®	148	Human: 82% Minipig: 82% Mice: 83%

mAB Subcutaneous Bioavailability Challenge



M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77

mAB Subcutaneous Bioavailability Challenge



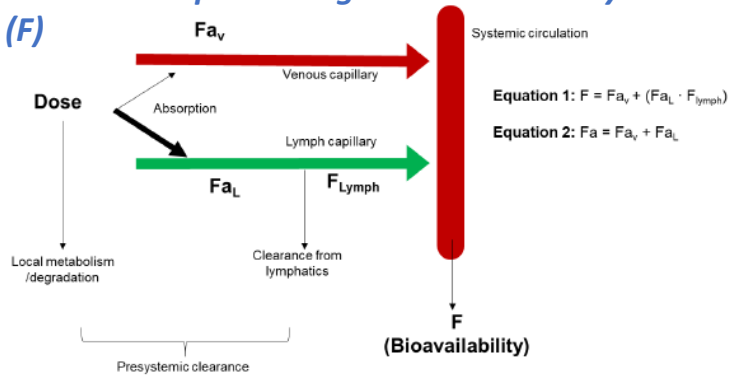
M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77

Subcutaneous Bioavailability Challenges

In Silico Modelling

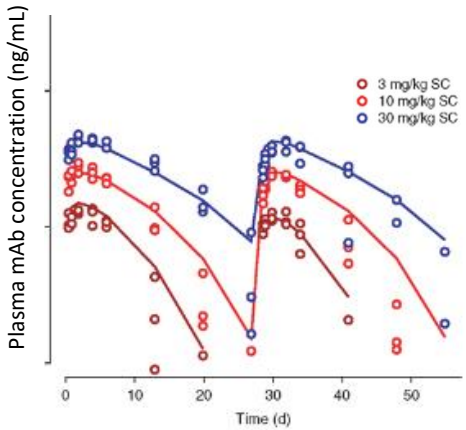
- In silico absorption modelling is successfully used in oral formulation development for compound selection, formulation design, specification setting and sometimes even in lieu of clinical bioequivalence studies
- Compared to oral, SC models are less well established, and are acknowledged as complex due to multiple, interrelated nonlinear pathways
- Empirical and mechanistic models have been developed
- **None can predict SC mAb bioavailability bottom-up**
- Aim to predict or understand factors affecting rate and extent of absorption and impact on PK profile
- Knowledge gaps/opportunities to improve the models have been proposed

Schematic representing SC Bioavailability (F)



F, bioavailability; Fa, fraction absorbed; Fa$_L$, fraction absorbed via lymph; Fa$_v$, fraction absorbed via venous capillary; F$_{Lymph}$, fraction escaping lymphatic clearance.

Example mAb SC PK profile

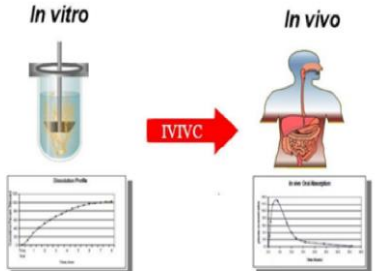


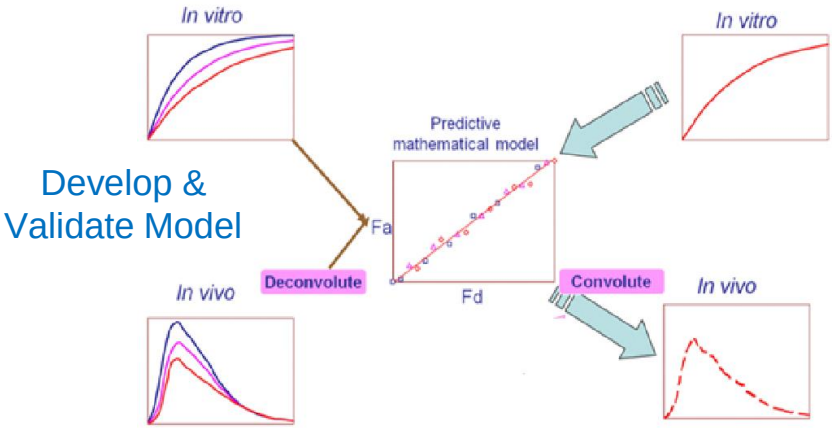
Reimagining Medicine

mAB Subcutaneous Bioavailability Challenge

Vision

- In-silico & In-vitro
- Translation of Bioavailability
- Bring Together Communities to Work on Needs





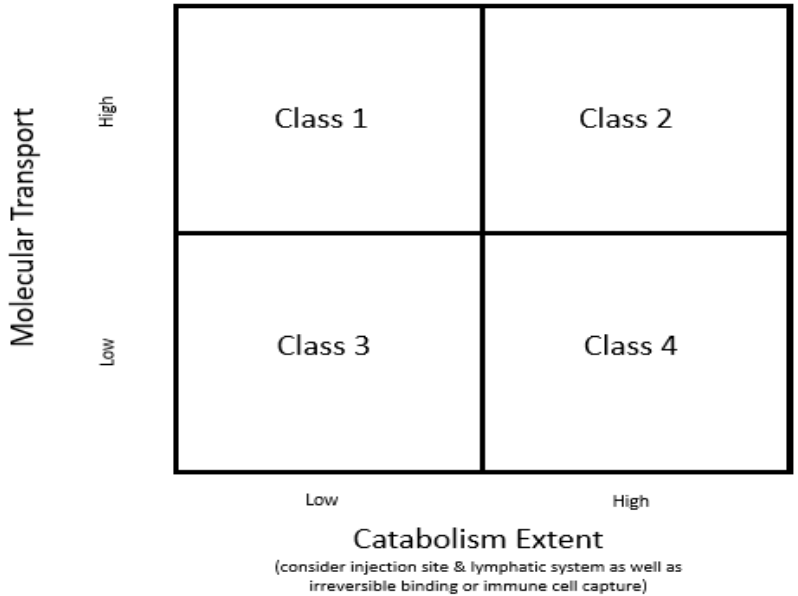
M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77

NOVARTIS | Reimagining Medicine

Subcutaneous Bioavailability Challenges

Open Challenge

Classification system concept for mAbs: molecular transport vs catabolism extent



mAB Subcutaneous Bioavailability Challenge

Provide three sets of data to validate hypotheses:

- Table capturing SC bioavailability data in human and corresponding preclinical species for a range of marketed mAbs.
- Excel document containing information on 26 marketed mAbs, physicochemical data, etc.
- Excel document containing PK data for the 12 therapeutic proteins described in the publication by Gill et al. (Gill et al. 2016).

Call to Action:

- Seeking to engage industry academia and government agencies to find solutions to advance capabilities in this area.
- On a case-by-case basis, access mAbs from member companies for investigations relevant to the objectives of this publication.
- On a case-by-case basis, provide letters of support for government research grants.
- Connecting researchers to other collaborators with complementary interests and capabilities that may be of mutual benefit.
- Compile any research findings on the challenge set and generate a publication after 2 years to provide an update on advances.

NOVARTIS | Reimagining Medicine

Summary

- Transition from IV to Subcutaneous Products is driven by patient and payer needs
- “Subcutaneous Drug Delivery & Development” Consortium formed to address known risks and gaps
- Multiple high-dose and high-volume formulation options are available to help transition your product to a more convenient patient-centric product
- The consortium has published an **“open”** SC bioavailability vision and challenge

Thank you

NOVARTIS | Reimagining Medicine

Acknowledgements

- TRD SC Group
  - Marie Picci
  - Karolyn Bechtold-Peters
  - Jorge Nerkamp
  - Isabel Ottinger
  - Sonia Morar-Mitrica
  - Maxime Gaillot
  - Robert Hormes
  - Sabine Adler
  - Harry Tiemessen
  - Stephane Olland
  - Many other colleagues in PHAD/CPP
- Subcutaneous Consortium
  - David Collins (Lilly)
  - Renee Tannenbaum (Halozyme)
  - Donna French (AZ)
  - Shawn Davis (AZ)
  - Sachin Mittal (Merck)
  - Ron Smith (Merck)
  - Advait Badkar (Pfizer)
  - Matt Burke (Radis Health)
  - Marie-Teresa Peracchia (Sanofi)
  - Neil Mathias (BMS)
  - Rajesh Gandhi (BMS)
  - Jennie Stevenson (Amgen)
  - Randy Mrsny (Bath University)

References

- Ahil Ganesh, Carolyn Heusser, Sudhakar Garad & Manuel Sanchez-Felix, Patient-centric design for peptide delivery: Trends in routes of administration and advancement in drug delivery technologies, Medicine In Drug Discovery, 2021

- David S. Collins, Manuel Sanchez-Felix, Advait V. Badkar, Randall Mrsny, Accelerating the development of novel technologies and tools for subcutaneous delivery of biotherapeutics, Journal of Controlled Release, 221, (2020), p. 475-482

- M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77