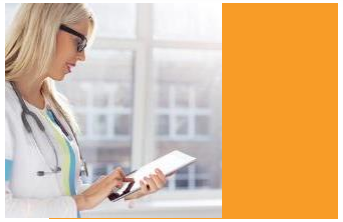
European Federation of Pharmaceutical Industries and Associations

Navigating Challenges in Subcutaneous Biologics: Advancing High and Ultra-High Concentration Technologies with a Patient-Centric Approach

Karoline Bechtold-Peters on behalf of the MQEG Biomanuf. WG on IV to SC Conversion



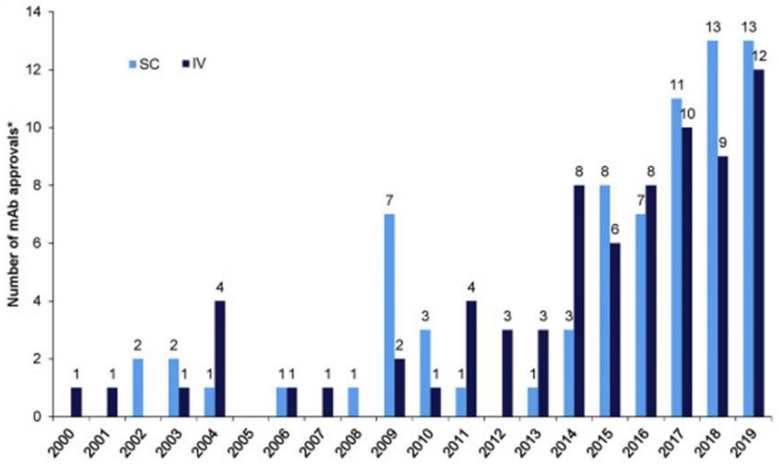

CASSS EU CMC Strat Meeting,
21.10.2024

What to expect?

- Setting the stage
- Challenges
- Workstream Goals
- Consensus and strategy

SETTING THE STAGE

The trend towards SC versus IV for Biologics...



Ca. 50% of the Biologics coming to market are applied SC nowadays

Source: Subcutaneous (SC) versus intravenous (IV) monoclonal antibody (mAb) approvals in the US from 2000 to 2019 (M. Sanchez-Felix, AdvDrugDelRev, 2020)apl

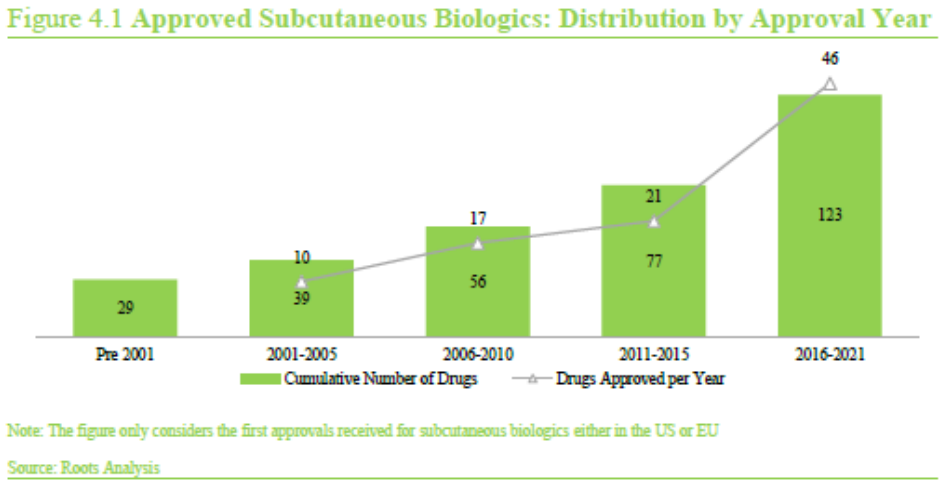
Further trends:

- extended interval dosing/reduced frequency
- Co-administration
- Co-formulation

This may contribute to increased needs for higher doses per treatment

Important to note: whilst self-application at home might be optimal for many indications, already application by HCP at doctor's office reduces substantially the burden compared to IV in hospital

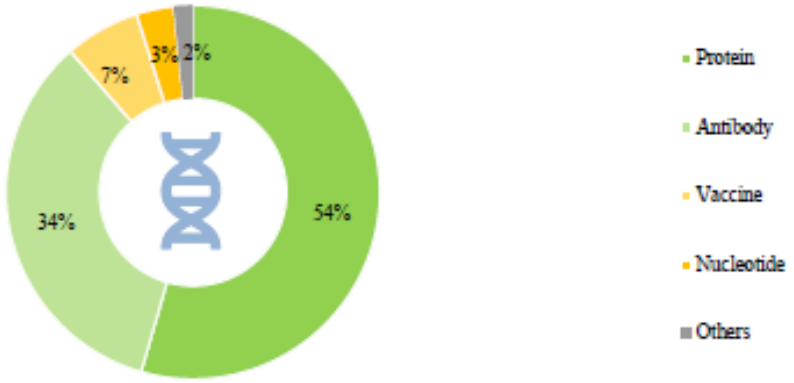
...drives increasing number of approvals of subcutaneous formulations essentially post 2016



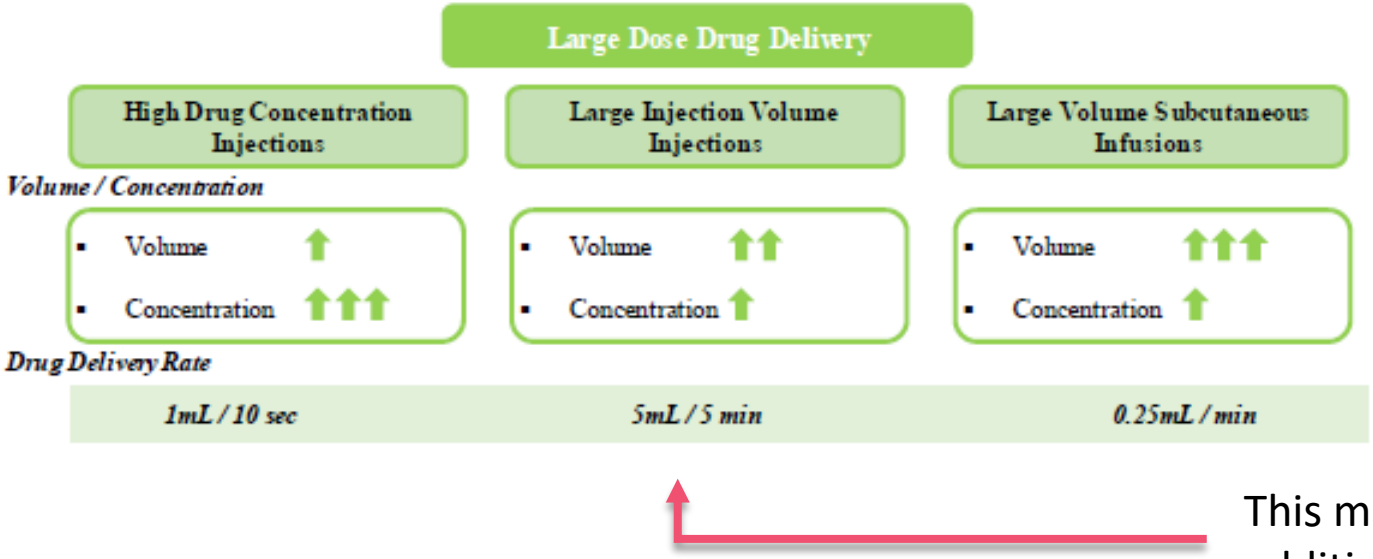
Distribution of the approved subcutaneous biologics on the basis of their year of approval (for subcutaneous formulation), only US and EU considered here

Source: Subcutaneous Biologics, Technologies and Drug Delivery Systems (4rd Edition), 2022 – 2035, Roots Analysis

Approved (2021) SC Biologics and Biologics-like Modalities by Type of Molecule...

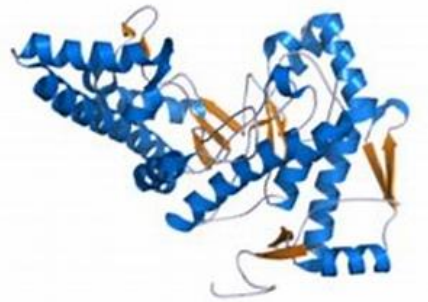


Note: The *Others* category include drugs which could not be classified in any of the abovementioned categories



...and Options for High Dose SC Treatments of such Molecules

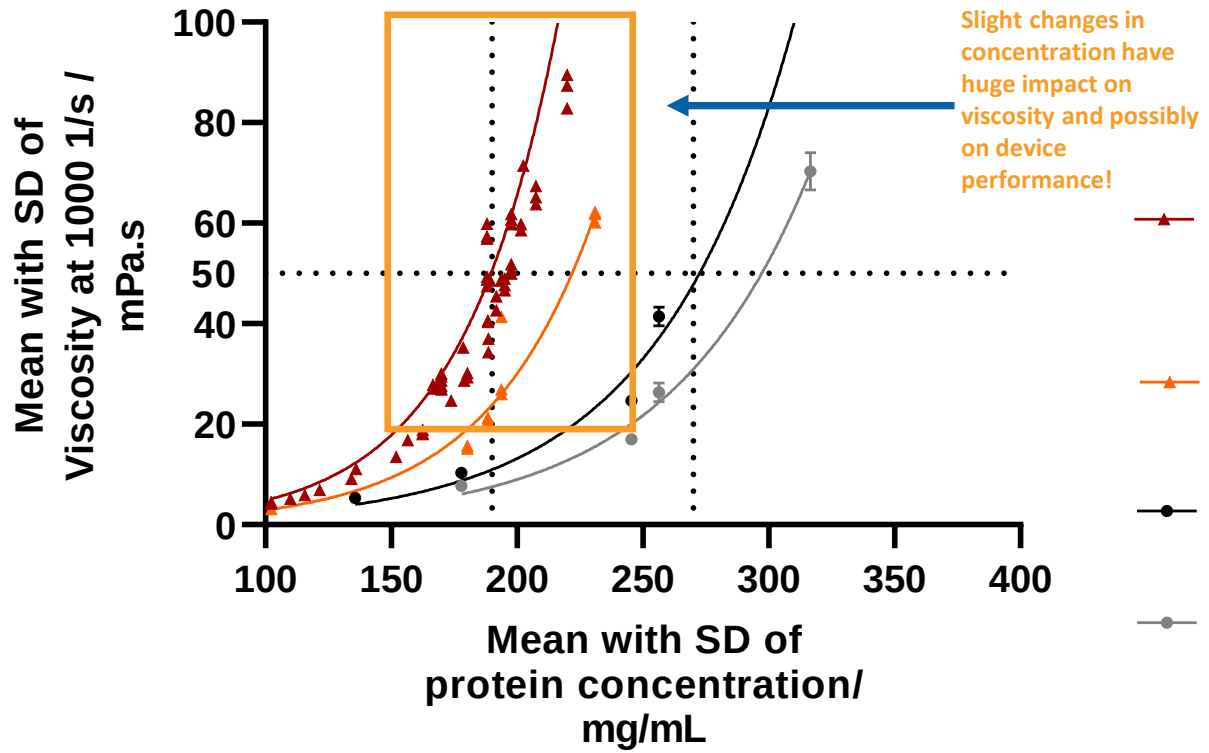
This may be enhanced by addition of hyaluronidase



Source: Subcutaneous Biologics, Technologies and Drug Delivery Systems (4rd Edition), 2022 – 2035, Roots Analysis

High concentration challenge: Protein concentration and viscosity – a nearly exponential** relationship and very much molecule specific...

mAb1 and mAb2 at 20°C and 30°C/32°C
Experimental data with exponential fit



	[Protein] mg/mL	Viscosity*/ mPa.s
mAb1	190	50
mAb2	270	50

...and temperature dependent

*all formulations were in 220mM sucrose, 20mM His-buffer pH 5.5, 0.04% PS20

** Mooney equation $\eta = \eta_s \exp([\eta] c /(1 - c/c_{max}))$

How can we lower the viscosity of highly concentrated mAb solutions?

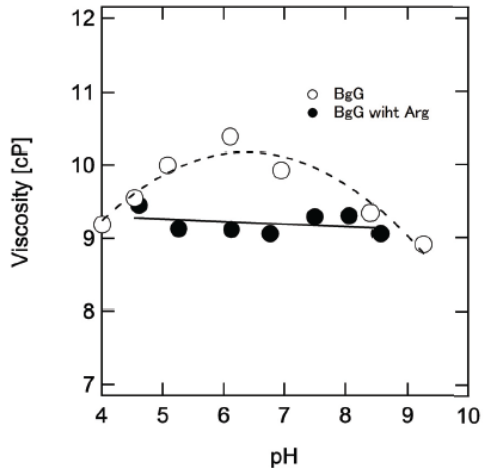
By increase of electrostatic repulsion / decrease of electrostatic attraction

- add inorganic or organic salts including charged amino acids (“electrostatic shield”)
- pI plays an ambiguous role

By decrease of hydrophobic/aromatic attraction

- Addition of chaotropes
- Addition of arginine (ArgHCl)

Multiface: histidine buffer (cation with aromatic properties and connects with protein by hydrogen bonds)



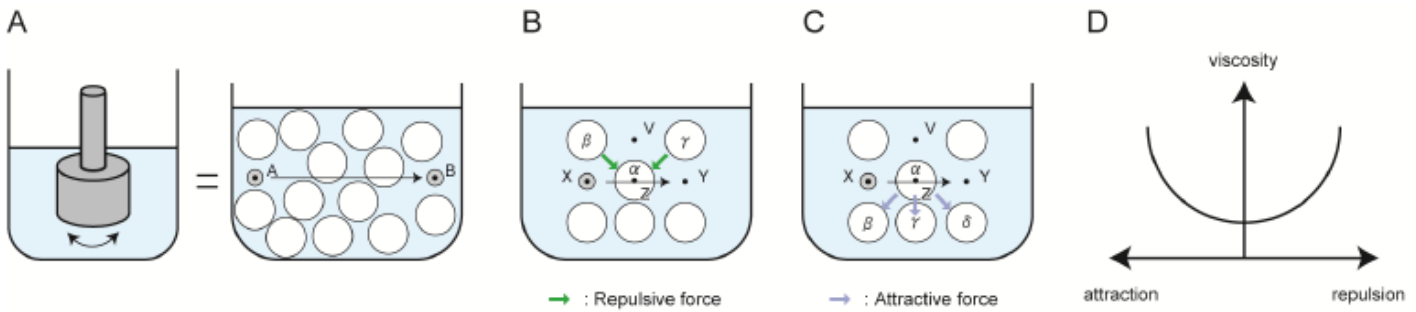
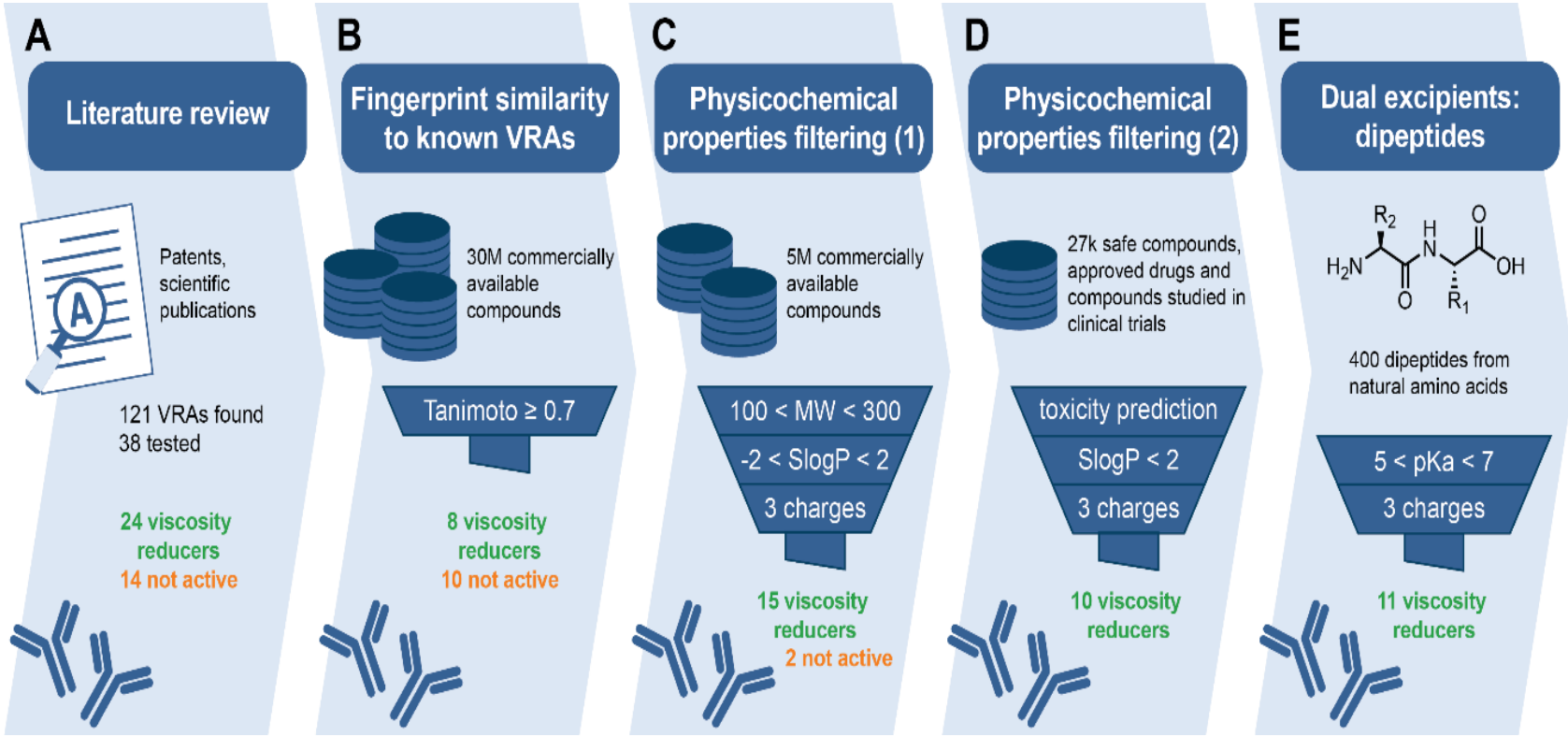


Fig. (6). Origin of viscosity. (A) Typical viscometer and the mechanism of viscosity. (B) A case of the repulsive force between α, β, and γ. (C) A case of the attractive force between α, β, γ, and δ. (D) The relationship between molecular interaction and solution viscosity.

T. Hong et al., Current Protein and Peptide Science, 2018

Systematic approach may generate yet unidentified candidates

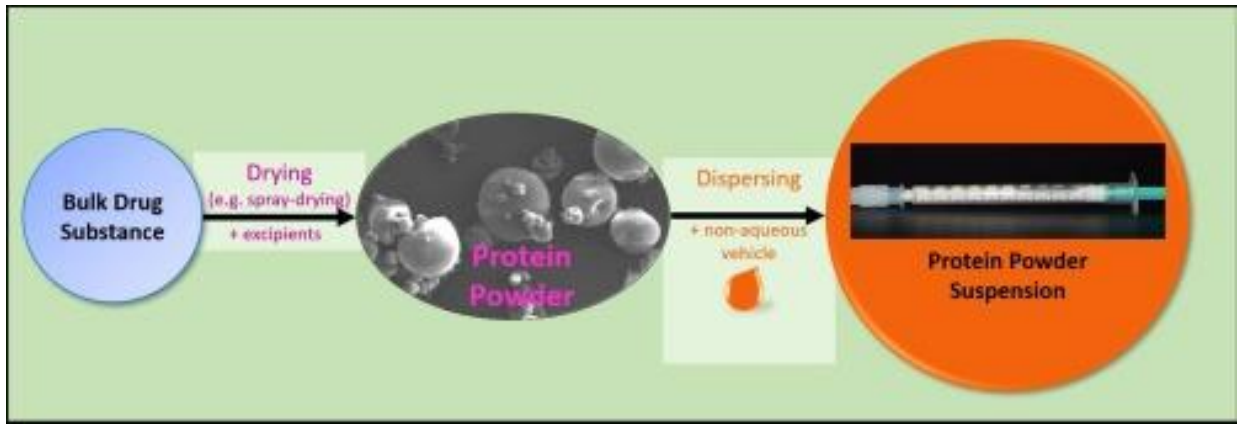


Workflow used to identify new viscosity-reducing agents. A different source of compounds and a different filter were used for each step. The viscosity of two model mAb solutions was measured in the presence of each compound tested. Overall, 68 of 94 compounds had a viscosity-reducing effects.

M. Proj et al, Computational and Structural Biotechnology Journal, Vol 20, 2022

Attractive alternative: Turning solutions into solids

- Via antisolvent processes
- Via aseptic spray-drying
- Via lyophilization & grinding
- Via mAb crystals
- ...and resuspension in non-aqueous vehicles (esters, oils)



TOLERABILITY AND PAIN

Tolerability considerations for *vehicles in non-aqueous* highly-concentrated biologics suspensions (NAS)

Vehicle	Viscosity (mPa s)	Parenterally approved?
Sesame oil	51-61 (25°C)	X
Safflower oil	52 (26°C)	X
Soybean oil	56 (25°C)	X
Castor oil Cottonseed oil	950 – 1100 (25°C)	X
Cottonseed oil	62 (24°C)	X
Triglycerides of caprylic and capric acid (MCT)	23-27 (25°C)	X
Propylene glycol diesters of caprylic and capric acids	9 (20°C)	
Triacetin	17.4 (25°C)	GRAS, tested in parenteral nutrition
Ethyl oleate	6 (25°C)	
Isopropyl myristate Isopropyl laurate	5 (25°C) 4.8 (25°C)	
PEG 200	48 (25°C)	X
Benzyl benzoate	8-9 (25°C)	X
Ethyl lactate	2 (20°C)	

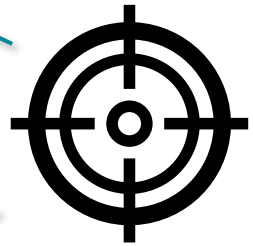
Vehicle	Viscosity (mPa s)	Parenterally approved?
Benzyl alcohol	5 (25°C)	X
Isopropyl alcohol	2.4 (25°C)	
Ethyl alcohol	1.2 (25°C)	X
Propylene glycol	39 (25°C)	X
Perfluorodecalin	6 (25°C)	
Perfluorohexyloctane	3.44 (25°C)	
Perfluorobutylpentane	1.05 (25°C)	

Source: adapted from C. Marschall et al, EJBP, 2021

Non-aqueous suspensions (NAS) for SC self-injection on the market e.g. with estrogen/estradiol or testosterone in castor oil or cottonseed oil.
In general well tolerated even upon chronic application with an autoinjector (ca. 10% show some local reaction from bruising to pain)
M.G. Figueiredo et al, J. Clin. Endocrin. & Metabolism, 2022

WORKSTREAM GOALS

Discuss & Share challenges with transition from IV to SC to the wider industry and Health Authorities

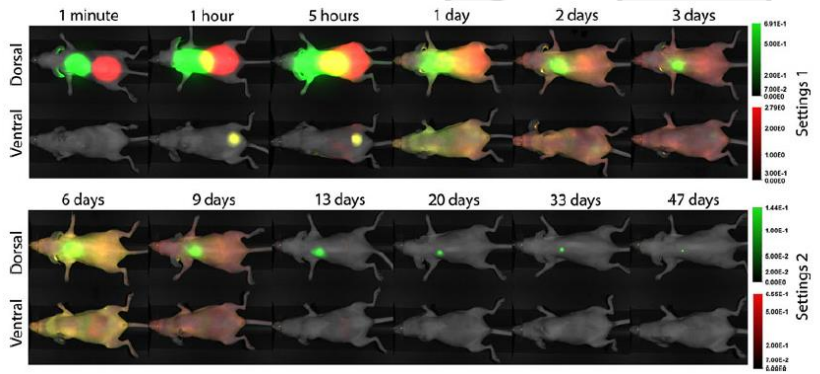


- New excipients (VRAs, non-aqueous solvents)
- Specification of subvisible particles with increasing concentration
- Specification of aggregates with increasing concentration
- Device component and Human Factor important as applied by patient
- Lack of robust PBMK Models representing the SC space
- How to bridge from IV to SC
- SC Bioavailability and behavior at injection site
- Immunogenicity of the SC space unknown

WORKSTREAM GOALS

Needed: more flexibility on specification setting for SC DP

- In the concentrated to ultra-highly concentrated SC preparations, there are more protein molecules per unit volume than traditionally. The previous specification of particles per volume or container creates an imbalance. The specification should consider the total applied amount.
- Adjusted specifications may be justified for the parameters
  - Subvisible Particles
  - Visible Particles
  - Aggregates
- Pharmacopoeial specifications may not apply
- Need to include aged material in clinical studies
- **Follow the approach of "patient-centric specifications" rather than follow pharmacopoeial standards**



Source: Filipe V et al, Pharm Res 2014; 31:216–227

A High Threshold of Biotherapeutic Aggregate Numbers is Needed to Induce an Immunogenic Response *In Vitro, In Vivo*, and in the Clinic

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Abstract

Background and Purpose There is concern that subvisible aggregates in biotherapeutic drug products pose a risk to patient safety. We investigated the threshold of biotherapeutic aggregates needed to induce immunogenic responses.

Methods and Results Highly aggregated samples were tested in cell-based assays and induced cellular responses in a manner that depended on the number of particles. The threshold of immune activation varied by disease state (cancer, rheumatoid arthritis, allergy), concomitant therapies, and particle number. Compared to healthy donors, disease state patients showed an equal or lower response at the late phase (7 days), suggesting they may not have a higher risk of responding to aggregates. Xeno-het mice were used to assess the threshold of immune activation *in vivo*. Although highly aggregated samples (~ 1,600,000 particles/mL) induced a weak and transient immunogenic response in mice, a 100-fold dilution of this sample (~ 16,000 particles/mL) did not induce immunogenicity. To confirm this result, subvisible particles (up to ~ 18,000 particles/mL, containing aggregates and silicone oil droplets) produced under representative administration practices (created upon infusion of a drug product through an IV catheter) did not induce a response in cell-based assays or appear to increase the rate of adverse events or immunogenicity during phase 3 clinical trials.

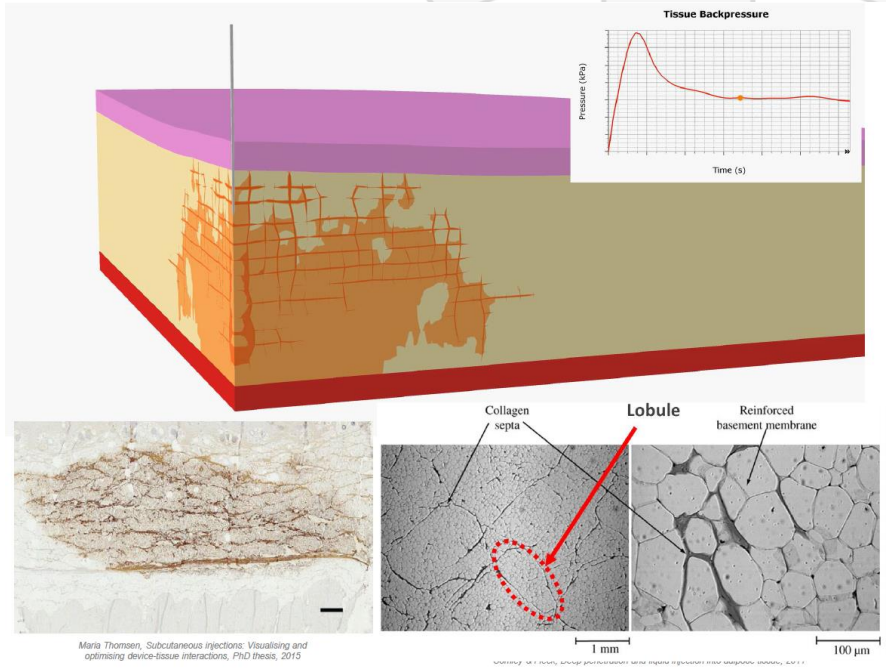
Conclusion The ability of biotherapeutic aggregates to elicit an immune response *in vitro*, *in vivo*, and in the clinic depends on high numbers of particles. This suggests that there is a high threshold for aggregates to induce an immunogenic response which is well beyond that seen in standard biotherapeutic drug products.

Keywords anti-drug antibody (ADA) · cytokine secretion · IgG · immune response · immunogenicity · *in-vitro* · monoclonal antibody · PBMC · protein aggregation · proteins · subvisible particles · threshold · transgenic mouse

WORKSTREAM GOALS

Explore and agree: on factors that Influence Bioavailability for SC DP

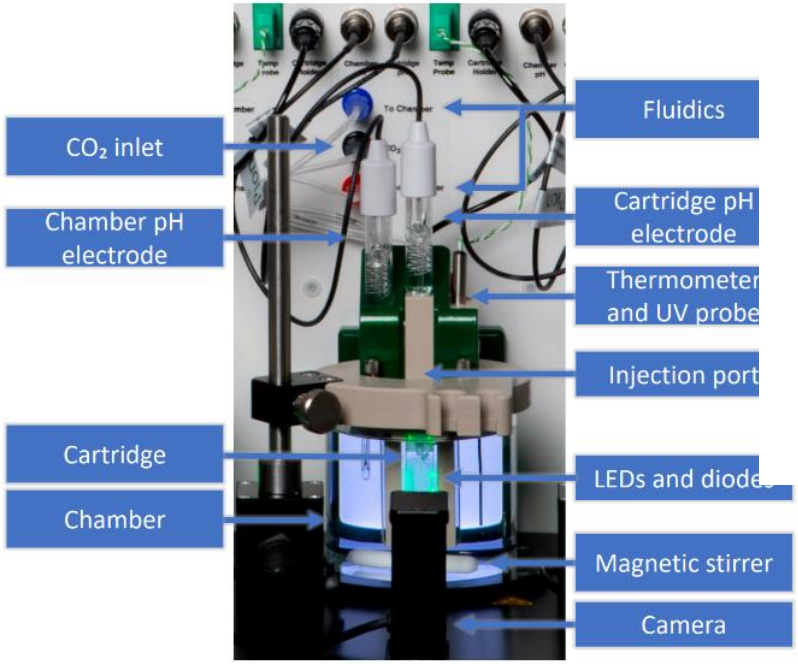
- The bioavailability from the SC Space is not really predictable at this time.
- There are various models in development, such as a Lymphatics-on-the-Chip model, which are very promising.
- **Sharing data and discussing with the authorities about the acceptance of such models would be helpful.**



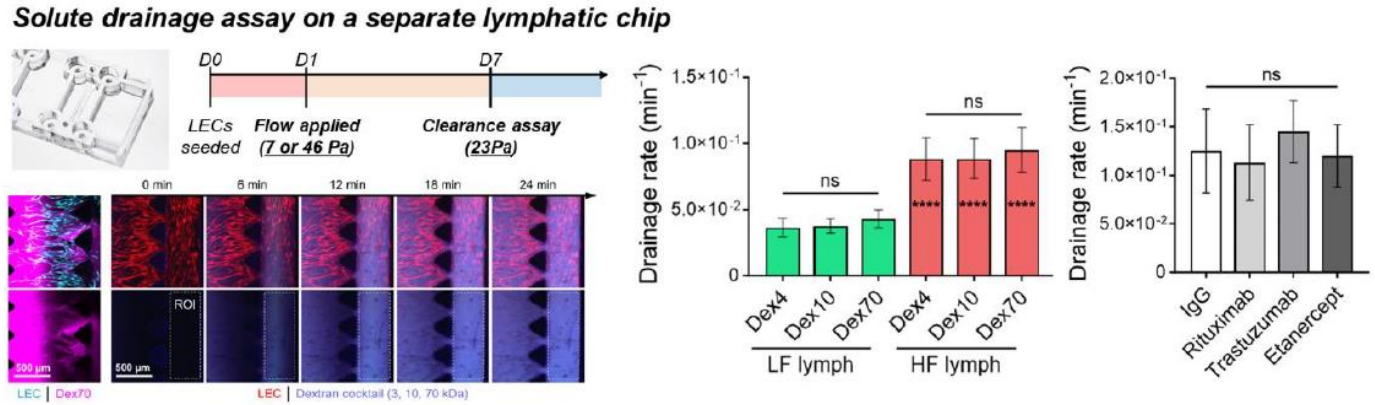
Source: Presentation by Joel Gresham, Crux, at CASSS EU CMC Strat Meeting in Bruges, 2022

SCISSOR and Skin-on-the-chip model

Scissor N3 set-up

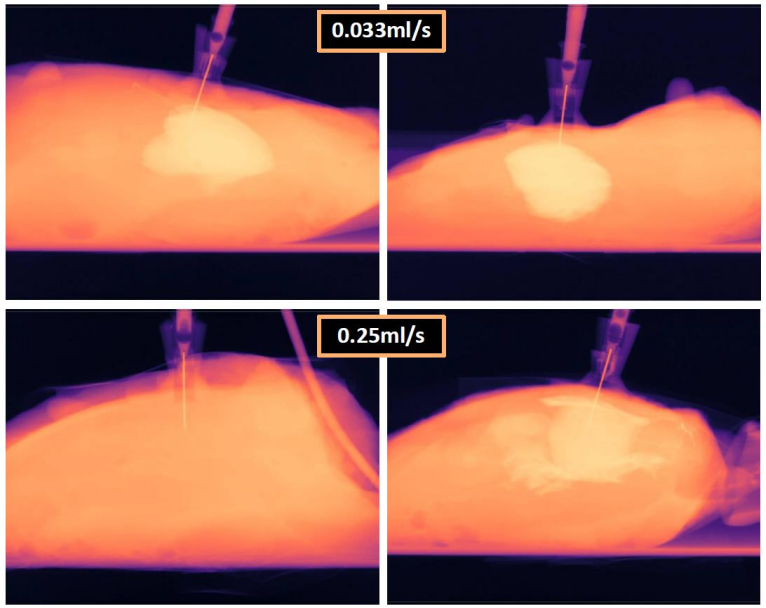


Skin-on-the-chip model



Discuss: Preclinical models to test SC products

- The famous discussions man versus minipig versus rat or versus other species, as well as normal minipig versus humanized minipig take place.
- **It would be desirable to achieve more consensus here and to develop common positions with the authorities.**



Source: Presentation by Joel Gresham, Crux, at CASSS EU CMC Strat Meeting in Bruges, 2022

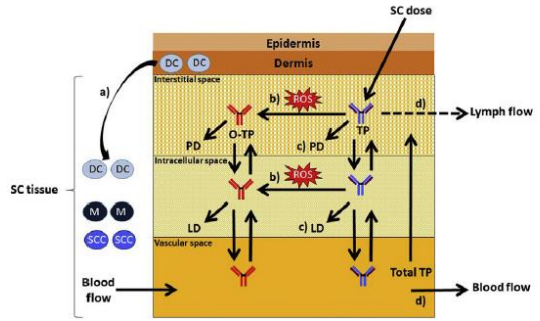
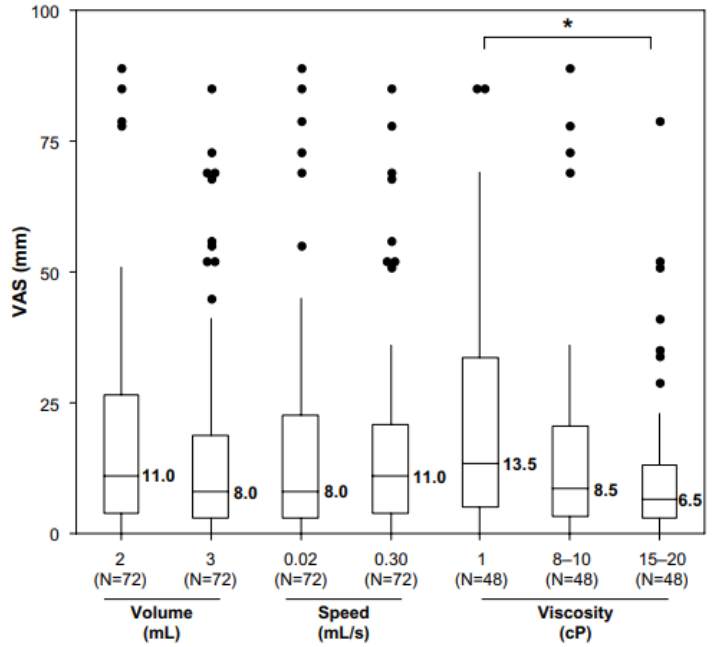


Figure 1. Physiological processes at the SC injection site. (a) Migration of DCs from the dermis to SC tissue due to penetration of the SC injection needle. (b) Potential oxidation of the TP by the ROS. (c) Proteolytic and lysosomal degradation of the TP in the SC interstitial and intracellular compartments. (d) Uptake of the TP by lymphatic capillaries (lymph flow) and blood vessels (blood flow). O-TP, oxidized TP; M, macrophages; PD, proteolytic degradation; LD, lysosomal degradation; SCC, subcutaneous cells.

Have a path forward: Pain factors

- The studies on the influence of factors on patient pain are not really clear. There seems to be a positive effect due to higher viscosity, while higher volumes result in a higher pain sensation.
- **It would be very much in the interest of patients if an IHI-supported project (EFPIA & EU), i.e. a focussed clinical study, could address this issue in a systematic manner**



Source: Berteau C et al, Medical Devices: Evidence and Research 2015:8 473–484

WORKSTREAM GOALS

Local tolerability & pain considerations – factors that might influence pain sensation

- **Dosing, Preparation, and Administration parameters**
  - Rate of injection, volume of injection, number of injections, frequency of dosing, subcutaneous injection depth, injection site, air bubble size, injection time
- **Device Parameters**
  - Needle size/shape/sharpness/quality, device type (pre-filled syringe, autoinjector, pen injector...), delivery mode (manual vs automated)
- **Formulation**
  - Buffer, excipients, pH, osmolarity/tonicity, preservatives, surfactants, viscosity, temperature, non-aqueous vehicle, hyaluronidase enzyme
- **User Attitudes**
  - Needle phobia, Injection apprehension, Perception of reliability & Perceived value of delivery system across gender
  - Injection administrator (self, caregiver or HCP)
- **Patient characteristics**
  - Patient age, gender, race
  - Body weight & age, skin thickness
- **Disease type**

Valuable reading: "Towards more tolerable subcutaneous administration: Review of contributing factors for improving combination product design", Neil Mathias et al, Advanced Drug Delivery Reviews Volume 209, June 2024, 115301

Align on: Fast to market strategies for transitioning from SC Vial or SC Syringe Product to SC Combination Drug Product in Device

- Need for limited PK studies instead of full blown Bioequivalence studies
- PFS to AI should not require bridging study
- Injection depth should be well understood and controlled
  → leverage to avoid PK studies
- **Acceptance of models/simulations of the injection manoever in lieu of clinical studies**
- **Acceptance of surrogates for injection devices**

Consensus Goal

- Publish individually and Collect what each company is working on into a consensus publication asking HAs for feedback; advance the debates in the team.

The group

- Lead: Karoline Bechtold-Peters (Karoline.Bechtold-Peters@novartis.com)
- AZ: Prashat Bhatia (prashant.bhatia@astrazeneca.com), Kate Harris (Kate.Harris@astrazeneca.com)
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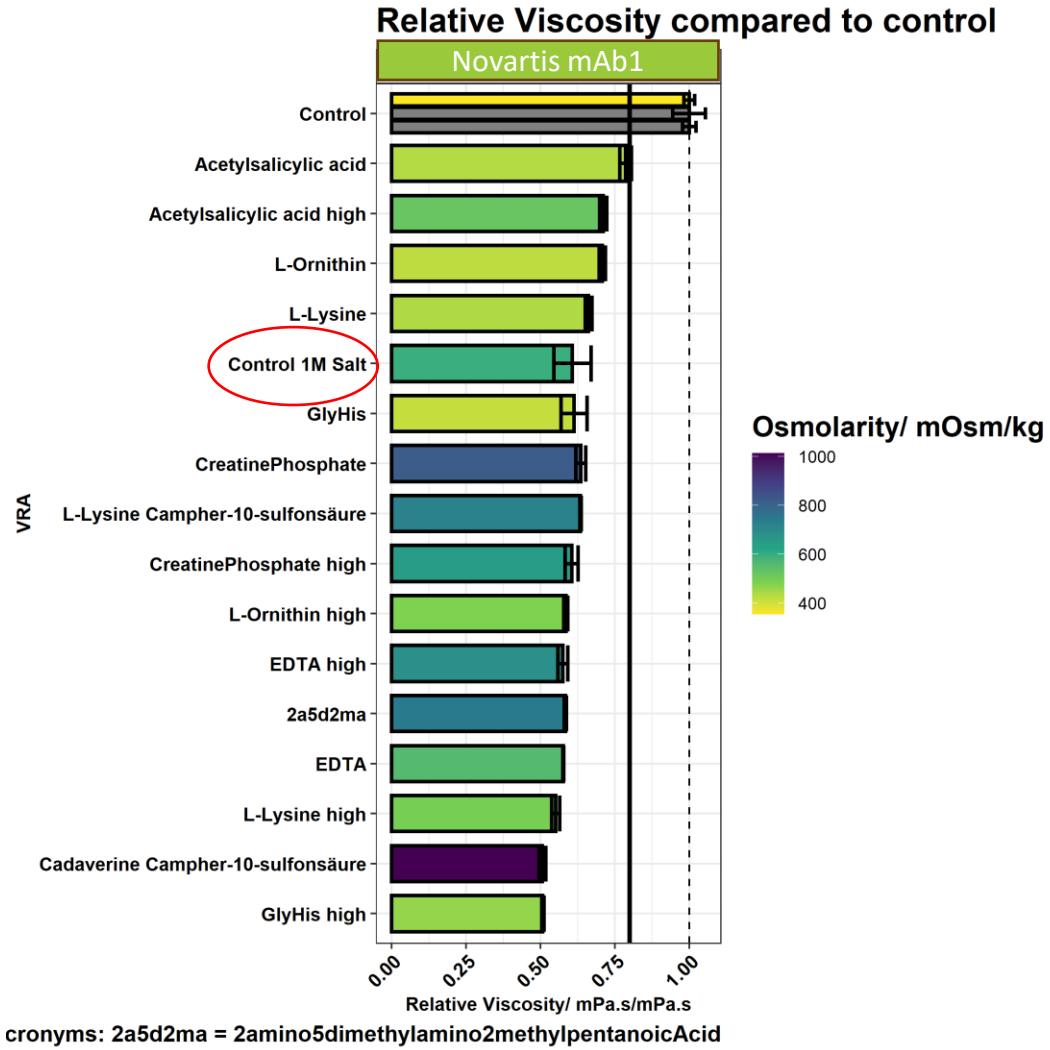
- Amgen: Andrew Lennard (alennard@amgen.com)
- Sanofi: Mieke Roels (Mieke.Roels@sanofi.com)
- Abbvie: interested, SME nomination pending
- MSD: Ashlesha Raut (ashlesha.raut@merck.com)
- GSK: George Crotts (george.h.crotts@gsk.com) , James Colandene (james.d.colandene@gsk.com)
- BMS: Jonathan Basch (jonathan.basch@bms.com)

Backup

Addition of VRAs (viscosity-reducing agents), example mAb1



Charge screening of attractive electrostatic interactions may lead to strong viscosity reduction, however impact on osmolality needs to be considered

Further reading:
M. Proj et al, Computational and structural biotechnology J., 2022
Z. Guo et al, Pharm Res, 2012

Conversion form IV to SubQ

- **Session on Satellite Symposium prior to CASSS EU CMC Strategy Meeting on October 17, 2022**
- **Program intended (see below) – could this be the topic of a new workstream along the lines of the symposium session?**
  - Implications of the device
  - Immunogenicity of the subQ space
  - Which models (in vitro/in vivo) do we have/are recommended and not recommended?
  - What role does SubQ play in patient centricity?
  - How can we reduce burden of bridging studies?
  - What do we know about factors contributing to bioavailability?
  - What do we know about factors contributing to pain?
  - Start with IV and then convert to SubQ?
  - FDA versus EMA?

Scientific Session on "Conversion of Intraveneous Infusion to Subcutaneous Application (ca. 20 min per talk, Q&A/Panel at the end ca. 30 min)

- **Subcutaneous Administration of Biotherapeutics: An Overview of Current Challenges and Opportunities (*Beate Bittner*, Roche, CH)**
- **CMC device and formulation & subQ Bioavailability considerations (*Marie Picci*, supported by Jörg Nerkamp, Manuel Sanchez-Felix and Karoline Bechtold-Peters, Novartis, CH/AT)**
- **Immunogenicity (or not) of biologics in the subcutaneous space (Sathy Balu-Iyer from University of Buffalo, USA)**
- **Modelling of subcutaneous injection & bioavailability to bridge IV/SubQ (*Joel Gresham and Max Dixon*, Crux, UK)**
- **Patient-centric approaches to bridge IV to subQ including prior knowledge (*Christian Mayer* from AGES, Austria)**
- **Q&A Panel discussion**

New Workstream