Développement des médicaments biologiques : exemples d'évolutions post Covid

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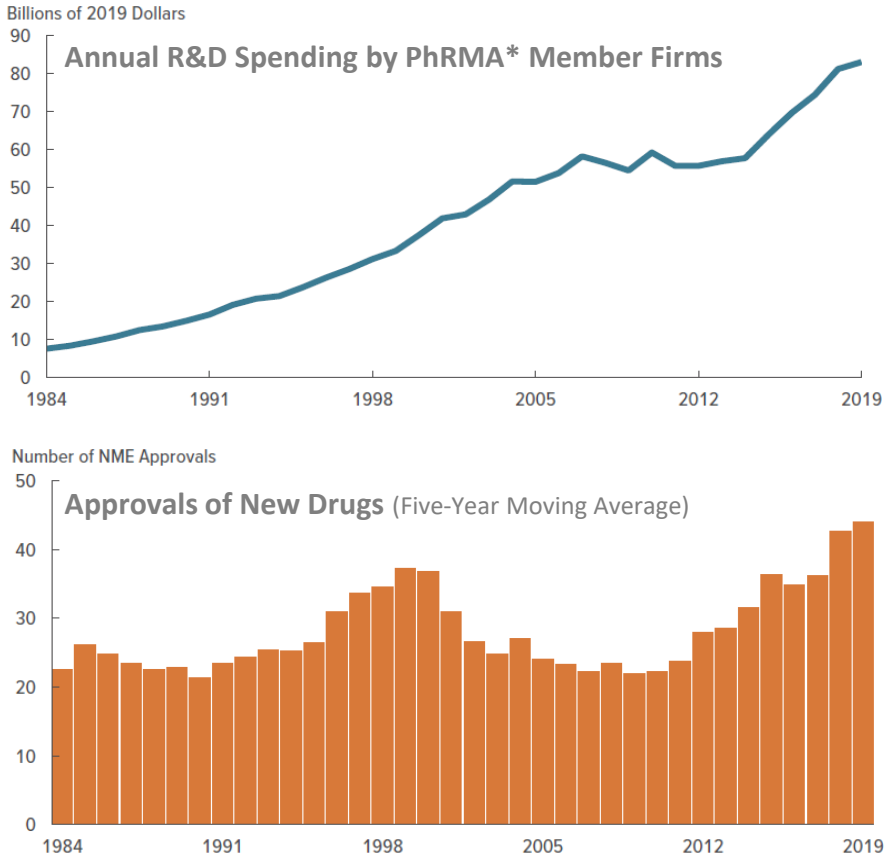
LES INNOVATIONS EN FORMULATION : LA CLÉ DE L'EFFICACITÉ DES NOUVEAUX MÉDICAMENTS

Covid -19 pandemic is changing pharmaceutical development

Long-term perspective: R&D spending increase with no clear link to new drug approvals



* PhRMA = Pharmaceutical Research Manufacturers of America
Source: Research and Development in the Pharmaceutical Industry - Congressional Budget Office, April 2021

Covid 19 pandemic: unprecedented pressure on biopharmaceutical companies

1. ***Strong pressure on the development*** of traditional products which is not expected to decrease
   ➜ Product development timeline for FIH (from lead mAb to IND) targeted at 12 months (instead of 18 months)
2. ***Accelerated CMC workflows*** to enable speed to clinical development by leveraging technological platforms
   ➜ Platform formulation for IgG1 mAb
3. ***Focus on alternatives to intravenous*** **(IV)** formulations with subcutaneous (SC) injections allowing administration in a non-clinical setting
   ➜ SC is becoming a main component of Phase 1 and expansion trials

Outlines

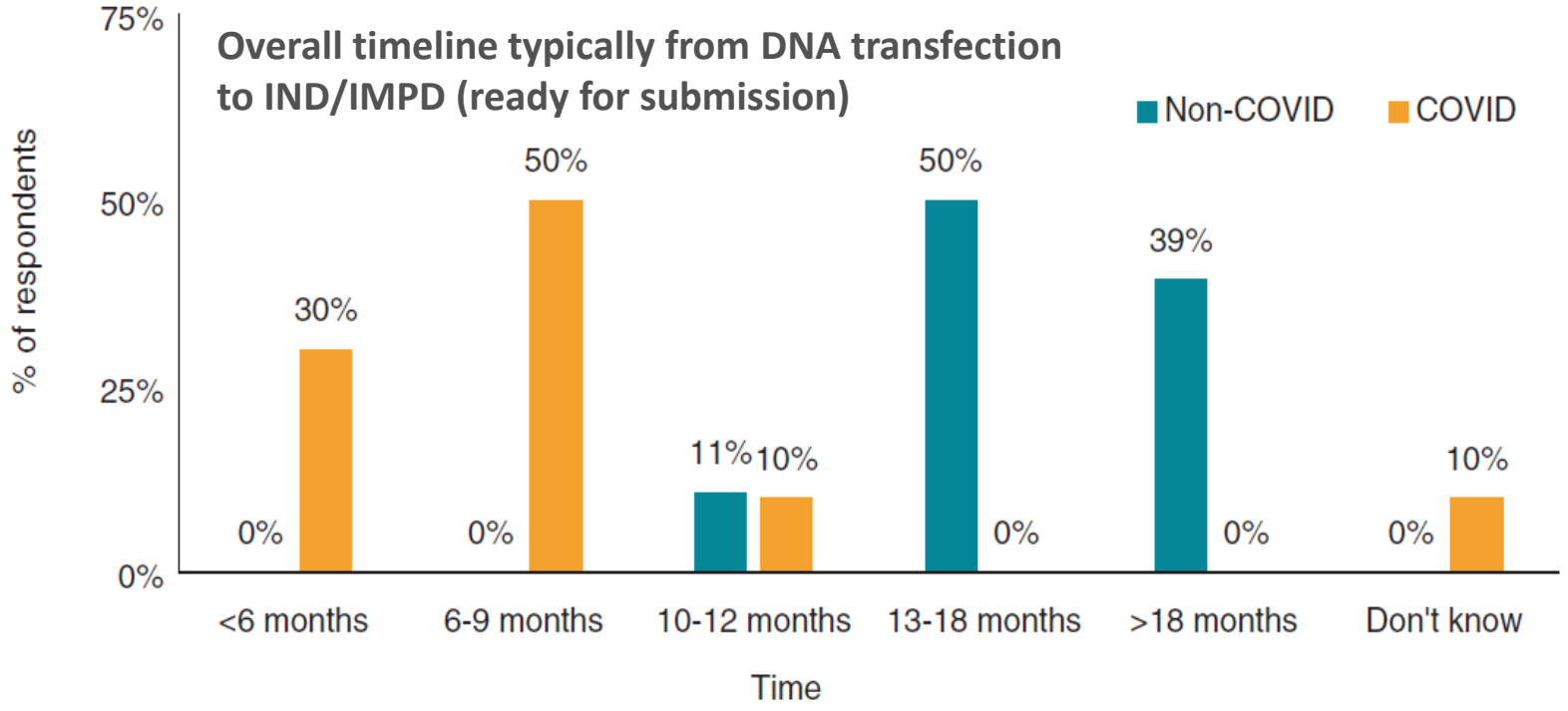

Accelerated development timeline
Formulation platform
Transitioning to SC administration

Speed to clinic benchmarking survey - Covid-19 vs “standard” programs

Timeline from DNA (i.e. transfection) to IND/IMPD (ready for submission) greatly accelerated for Covid 19 programs

Multi companies survey from 35 biopharmaceutical company members of BioPhorum*

- Significant reduction of the timeline for Covid-19 program (6-9 m) compared to standard program (13-19 m)
- The slowest Covid-19 program # fastest standard program



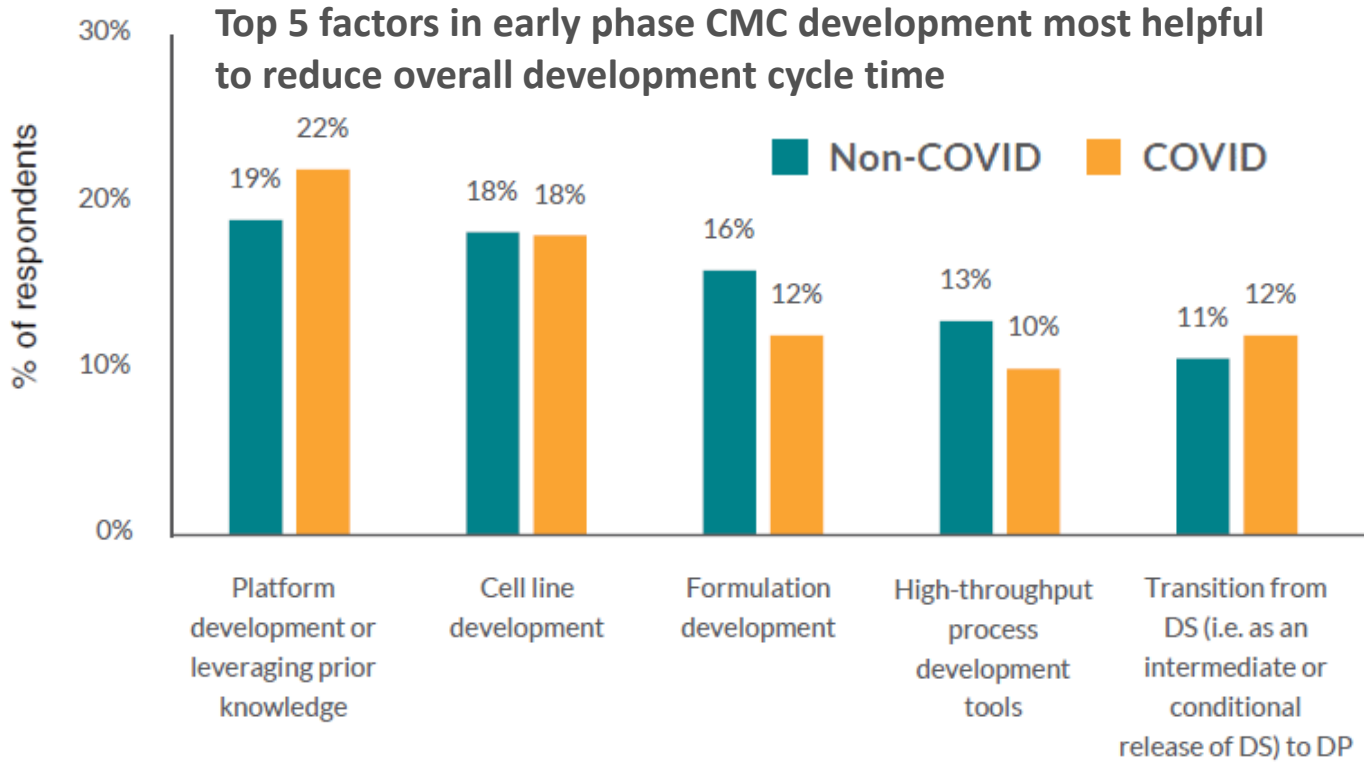
* Higgins, Matthew F., et al. "Accelerated CMC workflows to enable speed to clinic in the COVID-19 era: A multi-company view from the biopharmaceutical industry." Biotechnology Progress (2022)

Speed to clinic benchmarking survey - Covid-19 vs “standard” programs

Multi companies survey from 35 biopharmaceutical company members of BioPhorum*

Top 5 factors in early phase CMC development that help reduce overall development timeline:

- Platform development or leveraging prior knowledge is key to accelerate IND/IMPD (ready for submission)
- The top 5 factors are unchanged between the Covid-19 and the standard programs



* Higgins, Matthew F., et al. "Accelerated CMC workflows to enable speed to clinic in the COVID-19 era: A multi-company view from the biopharmaceutical industry." Biotechnology Progress (2022)

Factors for reducing phase 1 timeline during the Covid-19 pandemic

Acceptance of business risks (not product quality or patient safety) is key

- ***Combination of a well-known production host (CHO)*** and ***well-established manufacturing*** technologies
  - Alternative hosts (yeast, E. coli …) increase safety risk resulting from variants, unusual glycans and host cell proteins
  - Highly productive cell line and larger bioreactor using single-use technology are preferred for rapid clinical production
  - Transient expression culture (clone pool) is engaged at pilot scale (>100 L) to produce materials to support downstream process, formulation and analytical developments, and possibly for toxicology studies
- ***Platform process for phase 1*** clinical material
  - The fastest process development strategy is preferred (business risk) with process steps offering good portability to other manufacturing facilities and/or CDMOs.
  - Restrict the use of raw materials to those that have already been tested and are available, as well as for container closure materials by using a platform
- ***Accommodate the drug*** **product configuration** with target dose and route of administration (when there are known)
  - Freeze-dried or liquid (frozen) drug product at conservative concentration #50 mg/mL
  - Platform primary container system (glass vial)
- ***Other drivers*** associated with acceptable business risks to contribute to accelerating the overall timeline
  - GMP processing at risk i.e. before cell bank testing complete
  - Minimal product quality for early batches
  - Rolling IND filing

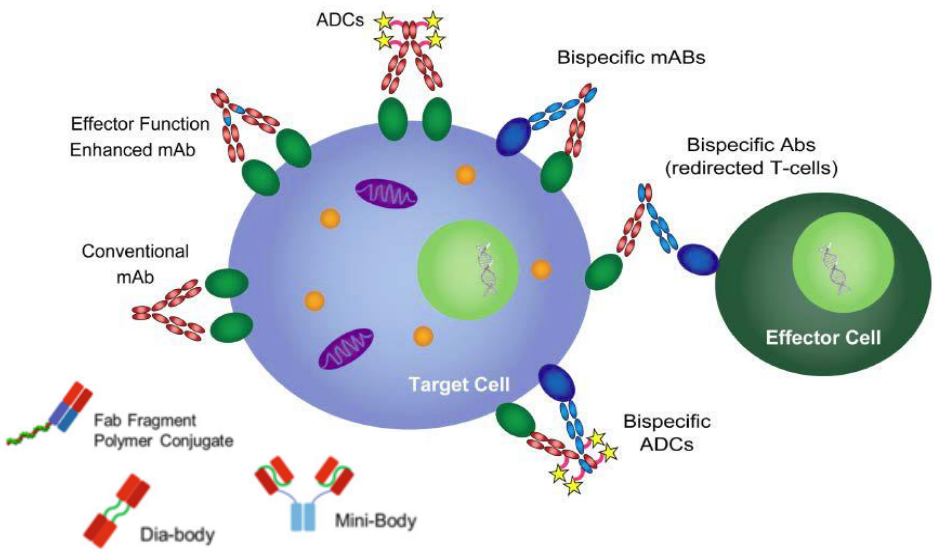
* Kelley, Brian. "Developing therapeutic monoclonal antibodies at pandemic pace." Nature biotechnology 38.5 (2020): 540-545.

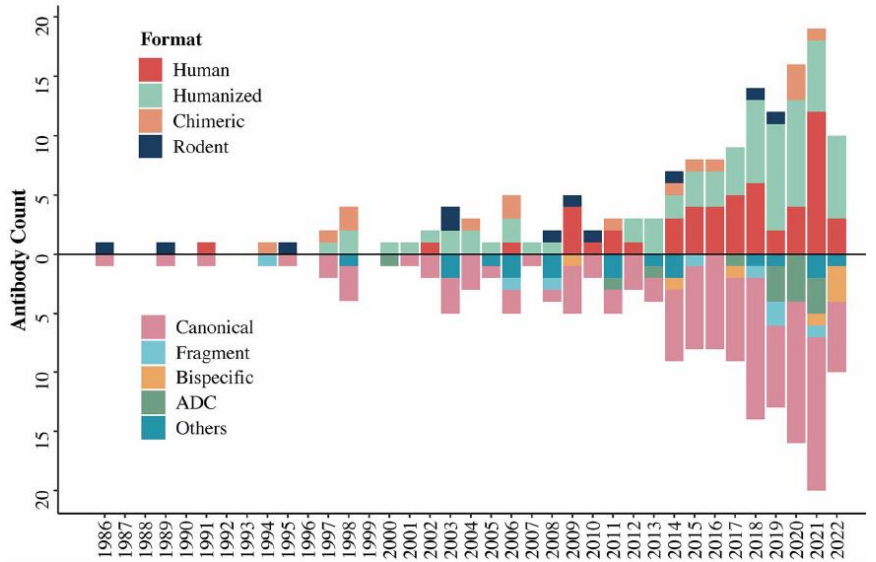
Beyond canonical IgG1, new modalities are increasingly being developed

Development framework should be continuously adaptive to new modalities (molecular scaffold, dosage form…)

New mAb modalities to preserve the benefits of conventional mAb (half-life, specificity) while improving efficacy (target binding, tissue penetration) and safety (reduced adverse effect / immunogenicity)

- New antibodies scaffolds: Bispecifics, ADC, Fab fragments, Mini-body…
- Engineered IgG Fc:
  - ➜ Silent effector function: IgG1 LALA, IgG1 NNAS, IgG4 PE/P FALA, IgG1 N297A/Q Aglycosylated isotypes
  - ➜ Enhanced effector function: IgG1 DE/ADE/ADLE isotypes, IgG1 afucosylated isotypes
  - ➜ PK prolongation : IgG1 LS, YTE isotypes





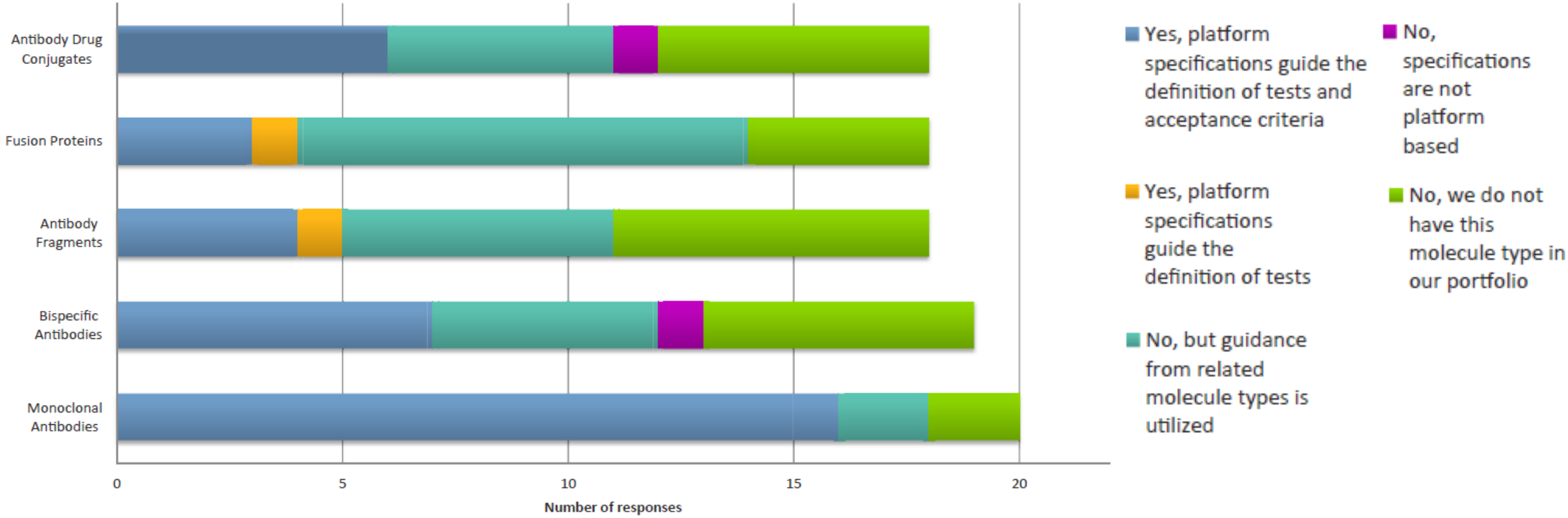
Number of ***different formats of mAb therapies*** for the year that they were first approved*

* Lyu, Xiaochen, et al. "The global landscape of approved antibody therapies." Antibody Therapeutics 5.4 (2022): 233-257
** Adapted from C. May et al. Biochemical Pharmacology 84 (2012) 11105-1112

Platform approach

Prior knowledge and experience for setting platform: mAb > bispecific Ab, ADC > Ab fragment > Fusion protein

Application of platform specifications - Results of IQ consortium survey*



* J. Kretsinger et al. Journal of pharmaceutical sciences 108.4 (2019): 1442-1452.

Formulation platform

Consensus on a set of few excipients and pH value has emerged over the past decade

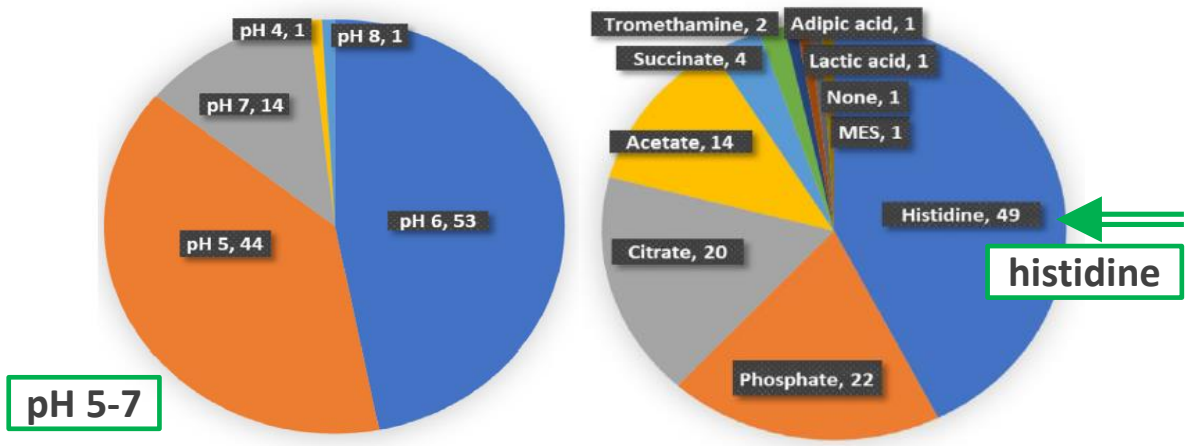
Excipients in commercially available antibody formulation

#	Excipients to Adjust Tonicity or Osmolality, and Lyoprotectants	Concentration, mg/mL
47	sucrose	25-100
25	sodium chloride	3-9
21	trehalose	8-100
9	sorbitol	35-50
4	mannitol	0.4, 12, 25, and 50
.../...		
121 Total		

Surfactant in commercially available antibody formulation

Surfactant	Concentration, mg/mL	#
None	-	12
Polysorbate 80	0.01	1
	0.04	1
	0.05	5
	0.1	14
	0.15	3
	0.2	26
	0.25 - 2	32
Polysorbate 20	0.04	1
	0.06	1
	0.08	5
	0.1	6
	0.2	7
	0.3 - 2	12
Poloxamer 188	0.2 - 1.5	4
		Total 131

pH range and buffers in antibody formulations, n=113



- ***Formulation platform*** for phase 1 clinical stage are commonly used, based on the ***most used excipients***
- ***Liquid formulations*** can be offered at ***moderate strength*** (#50 mg/mL) or ***lyophilized forms*** when stability is preferred to ensure acceptable ***shelf-life*** for the clinical study

* Strickley, Robert G., and William J. Lambert. "A review of formulations of commercially available antibodies." Journal of pharmaceutical sciences 110.7 (2021): 2590-2608.

Biotherapeutics transitioning to SC administration

Strong trend in favor of biotherapies administered by SC which becomes a main component for phase 1

Traditional IV administration, typically in clinic, may contribute to ***presure on healthcare systems and patients***

SC administration as an alternative has benefits such as reduced ***treatment time***, ***cost*** and ***adverse systemic effects*** and increased patient ***convenience and autonomy***

Biotherapeutics formulation being considered for SC combination therapy may have ***increased dosing complexity*** such as volumes and viscosities

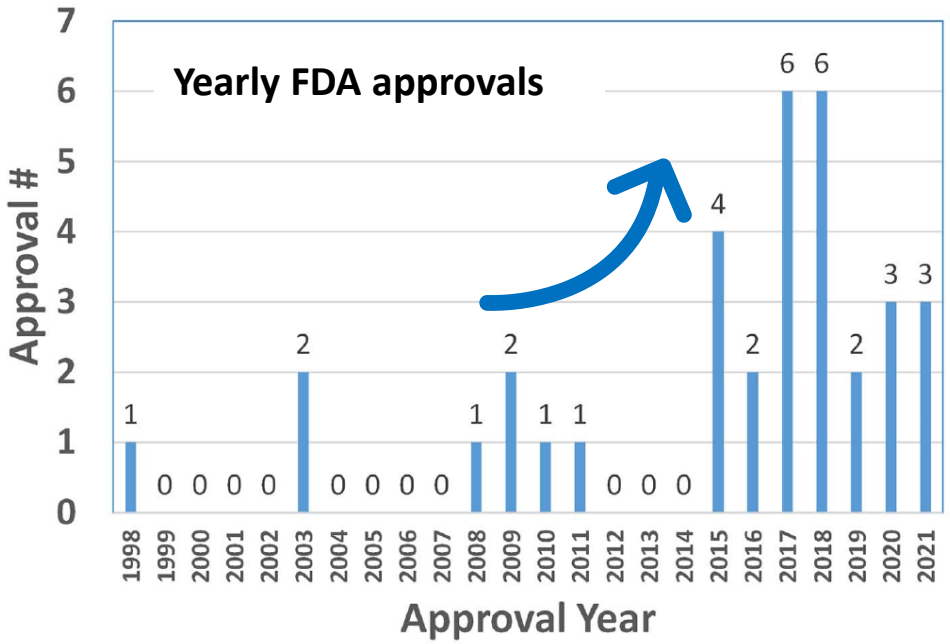
SC delivery systems such as ***pre-filled syringes*** and/or ***fixed-dose injectors*** enable self-administration of biotherapeutics

Subcutaneous drug products is an area of innovation for mAbs, specially for the technologies to enabling high-dose / high-concentration (HD/HV) delivery

* Collins, D. S., Sánchez-Félix, M., Badkar, A. V., & Mrsny, R. (2020). Accelerating the development of novel technologies and tools for the subcutaneous delivery of biotherapeutics. Journal of controlled release, 321, 475-482.

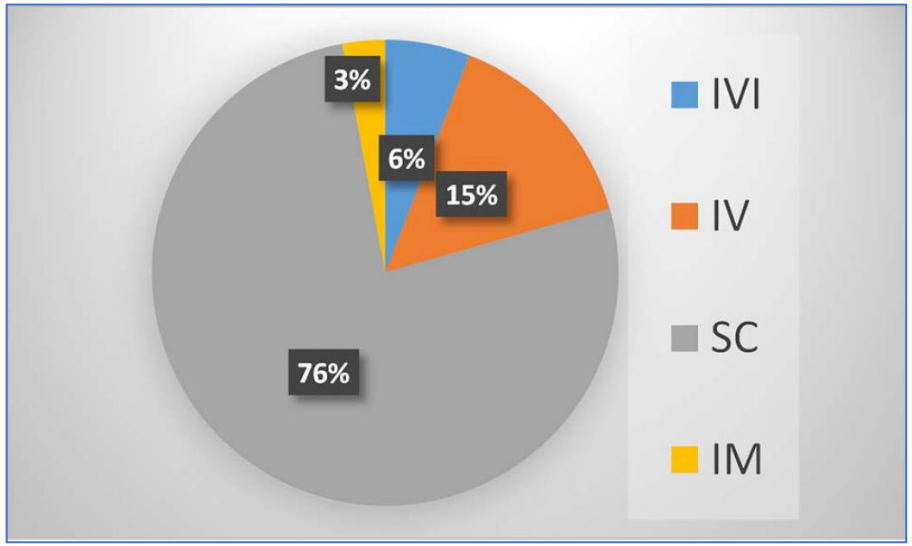
Biotherapeutics transitioning to SC administration

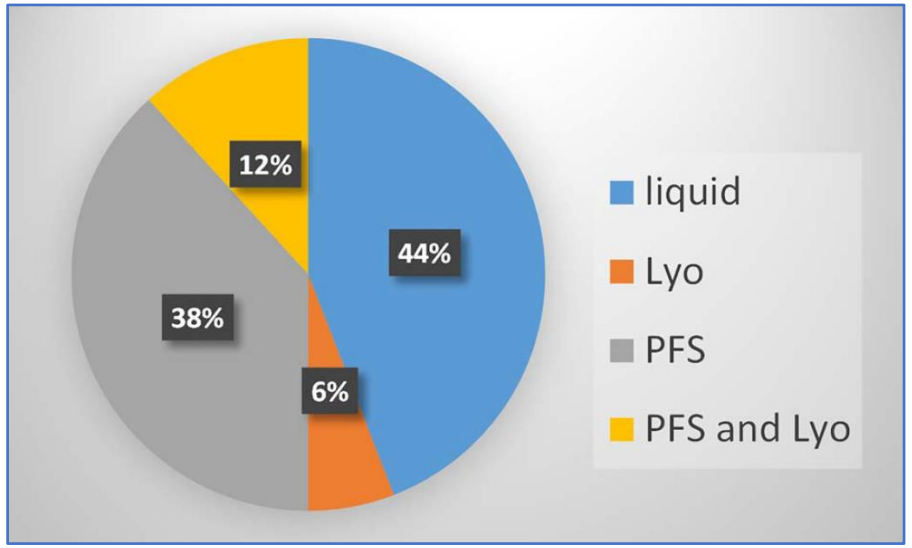
Therapeutic antibodies with high concentration formulation (>100 mg/mL) during 1998 – Oct 2021*



Route of Administration:

- IVI: Intravitreal;
- IV: intravenous;
- SC: subcutaneous;
- IM: intramuscular.





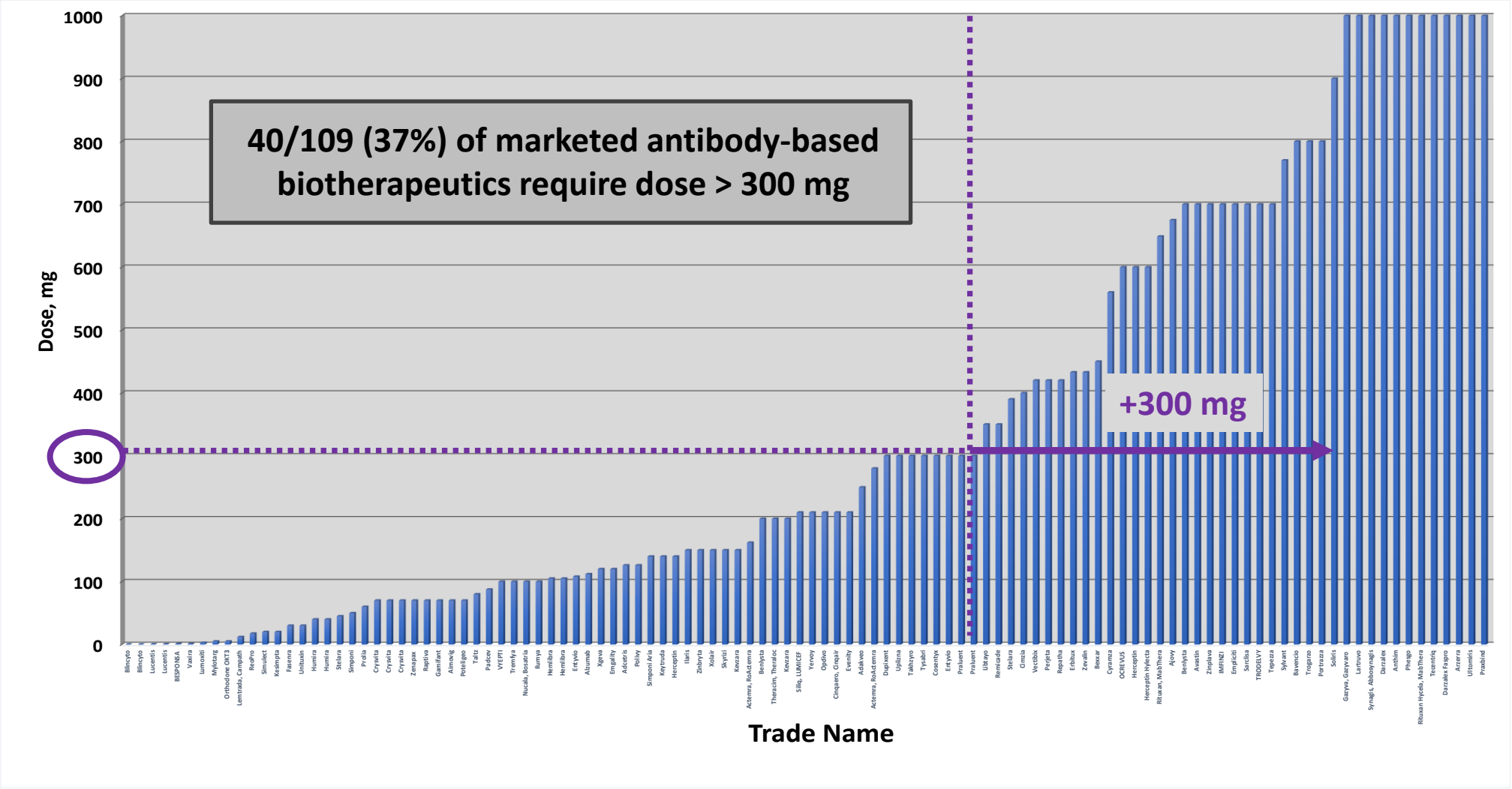
Dosage form:

- Lyo: lyophilized powder
- PFS: pre-filled syringe (including Auto Injector)

* Wang, Shawn et al. (2021) US FDA-approved therapeutic antibodies with high-concentration formulation: summaries and perspectives. Antibody Therapeutics 4.4, 262-272.

High-dose delivery is a challenge for the transition to SC administration

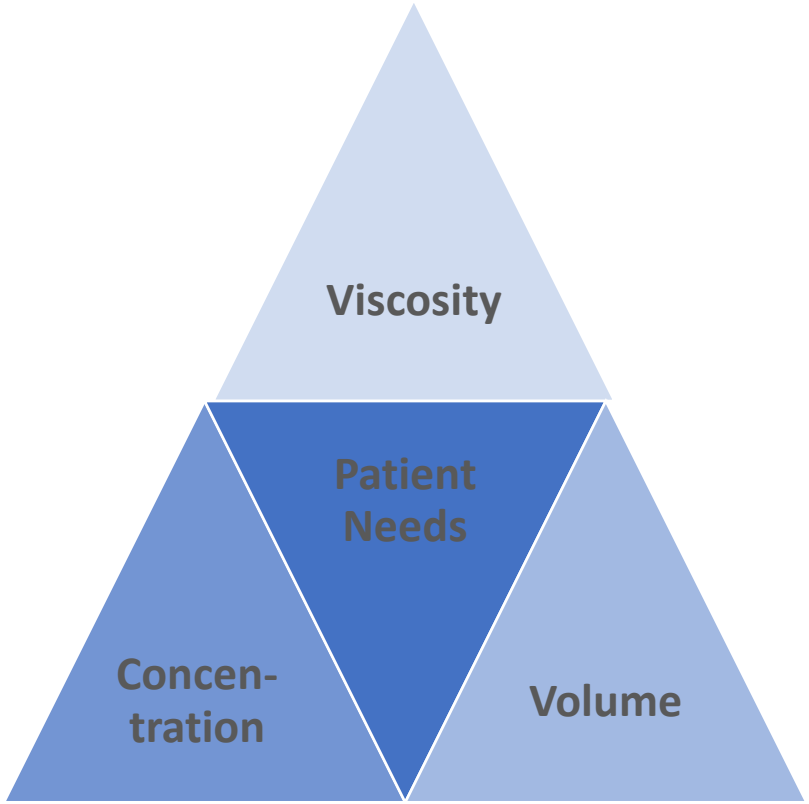
Increasing treatment options require doses which cannot be delivered by established SC dosage forms



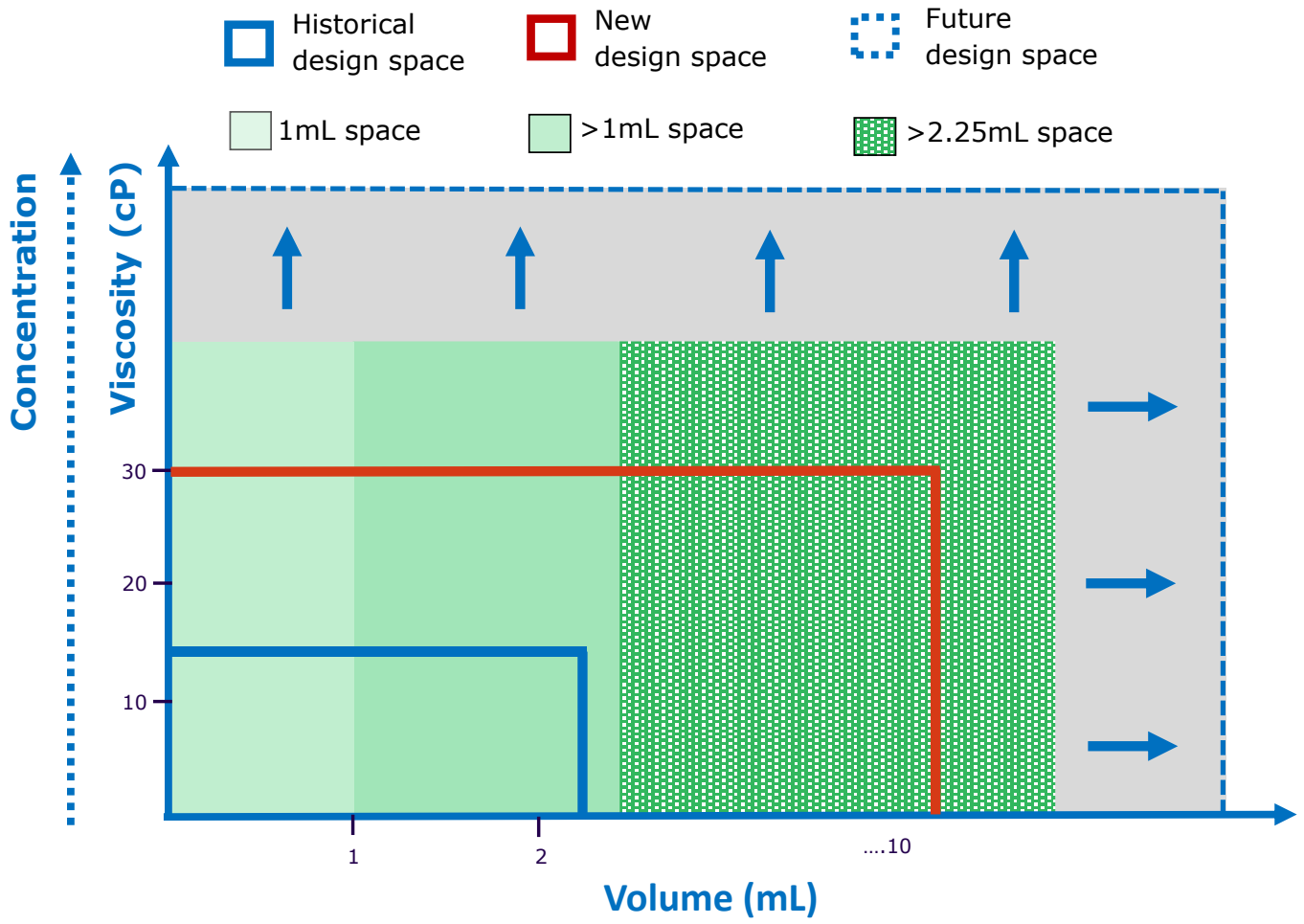
* Adapted from Martin, Kyle P., et al. "Trends in industrialization of biotherapeutics: a survey of product characteristics of 89 antibody-based biotherapeutics." Mabs. Vol. 15. No. 1. Taylor & Francis, 2023..

High dose / high volume subcutaneous delivery

Growing number of clinical trials with new drug product formulations and drug delivery systems aimed at pushing the boundaries of SC delivery



Viscosity/concentration/volume closely related to ***formulation*** and ***device combination***



* Adapted from Wendy Woodley; AAPS, Biotechnology Conference, 10/18/21

Differentiated SC delivery opportunities by dose

The dosage regimen is defined at a late stage of development and requires the CMC to develop the DP presentation before the dose range is confirmed

Dose (mg) ➜

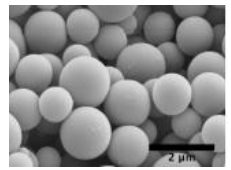
150 | 300 | 600 | 800 | 1000+

High Conc platform

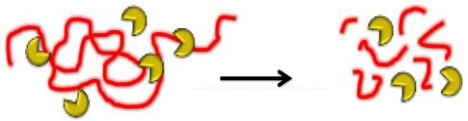
Large Volume delivery system

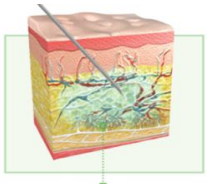
Supra-high concentration formulations ≤2 mL

Suspension in non-aqueous vehicle 350+ mg/mL



Hyaluronidase formulations (i.e. rHuPH20)

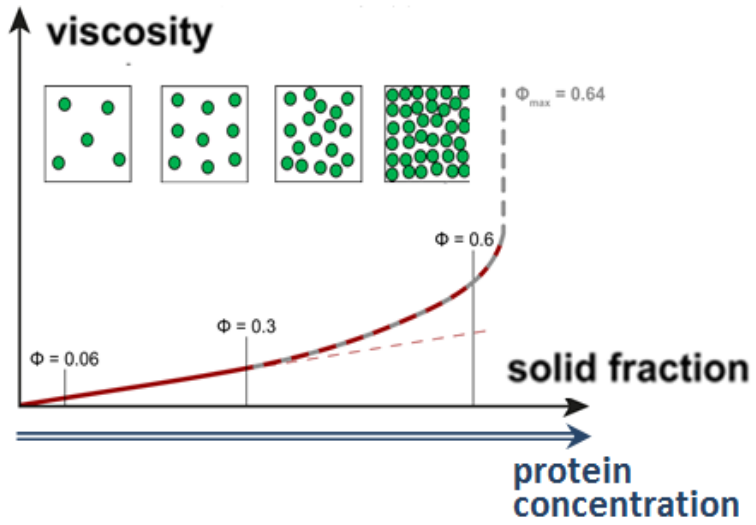


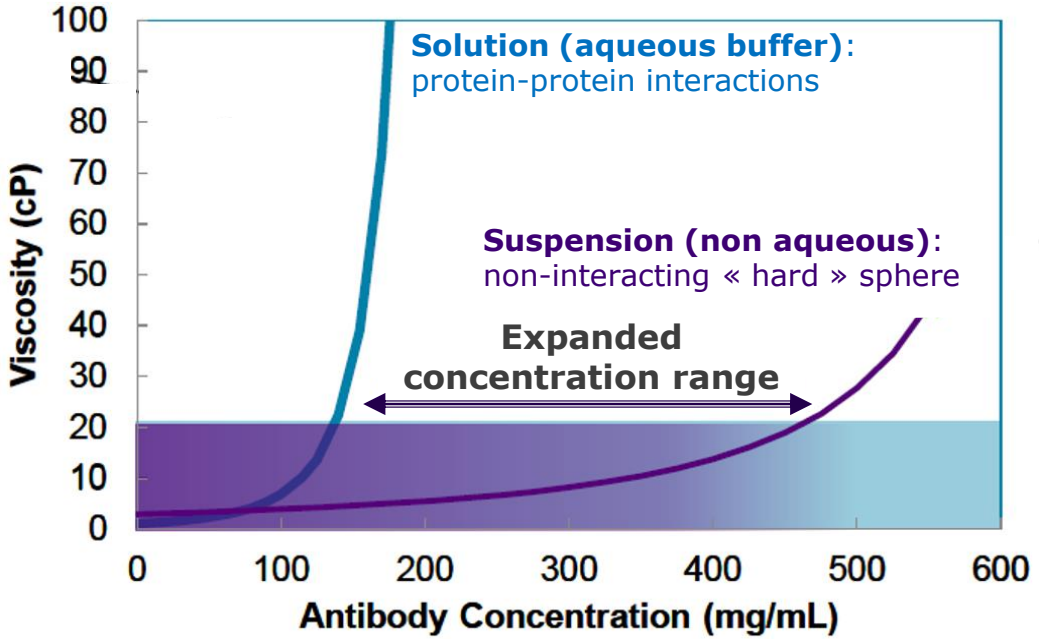


Temporarily cleave hyaluronan in the extracellular matrix and facilitate large volume infusion into SC

High concentration non-aqueous protein powder suspenion

A potential alternative providing lower viscosity vs aqueous solution at high concentration



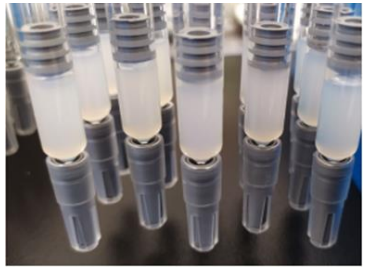


$$\eta = \eta_0 \left[1 - \frac{(\varphi)}{(\varphi_{max})}\right]^{-[\eta_{int}]\varphi_{max}}$$

* **Kriger-Dougherty modelisation**

➜ volume fraction of the solute

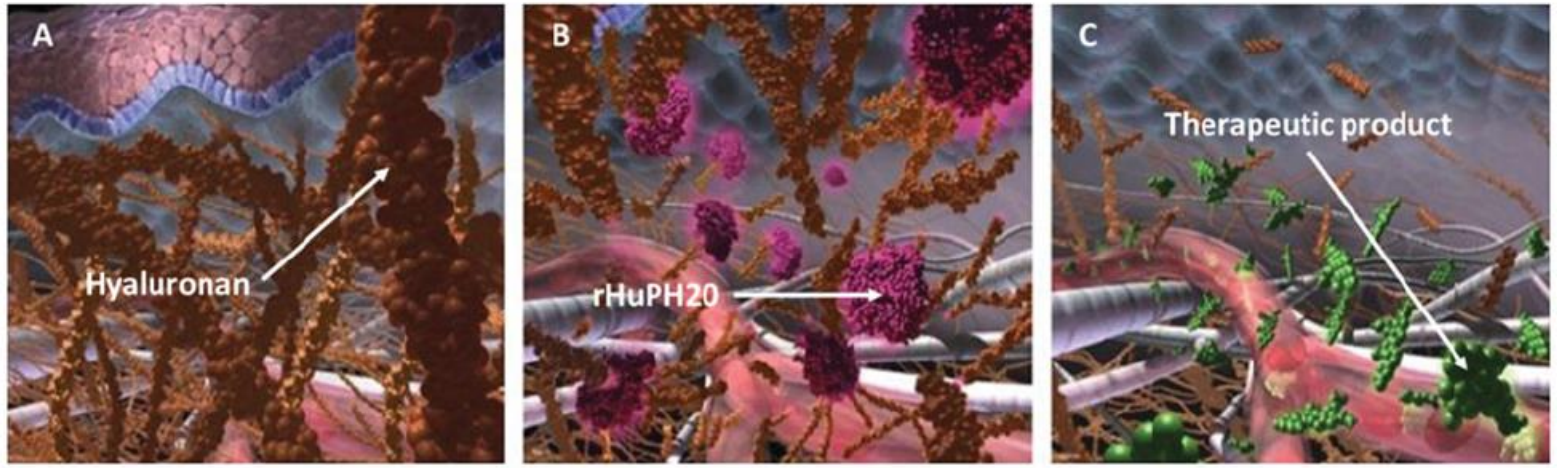
➜ vehicule solution viscosity



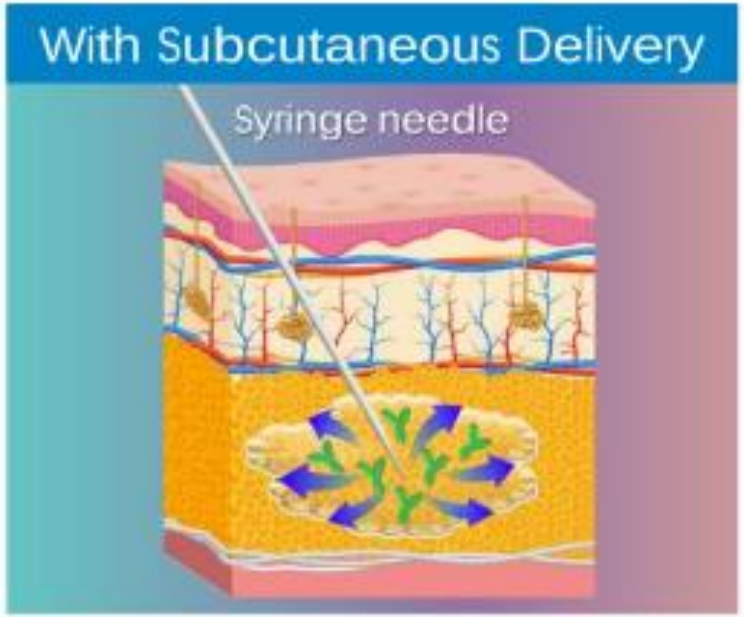
* Marschall, Christoph, et al. "Drug Product Characterization of High Concentration Non-Aqueous Protein Powder Suspensions." Journal of Pharmaceutical Sciences 112.1 (2023): 61-75.

SC administration using recombinant human hyaluronidase PH20

ENHANZE™ drug delivery technology



rHuPH20 mechanism of action. (A) Hyaluronan creates a resistance to bulk fluid flow and limits large volume SC drug delivery, dispersion, and absorption (B) rHuPH20 depolymerizes hyaluronan, (C) facilitating SC bulk fluid flow and increasing the dispersion and absorption of co-administered therapeutics



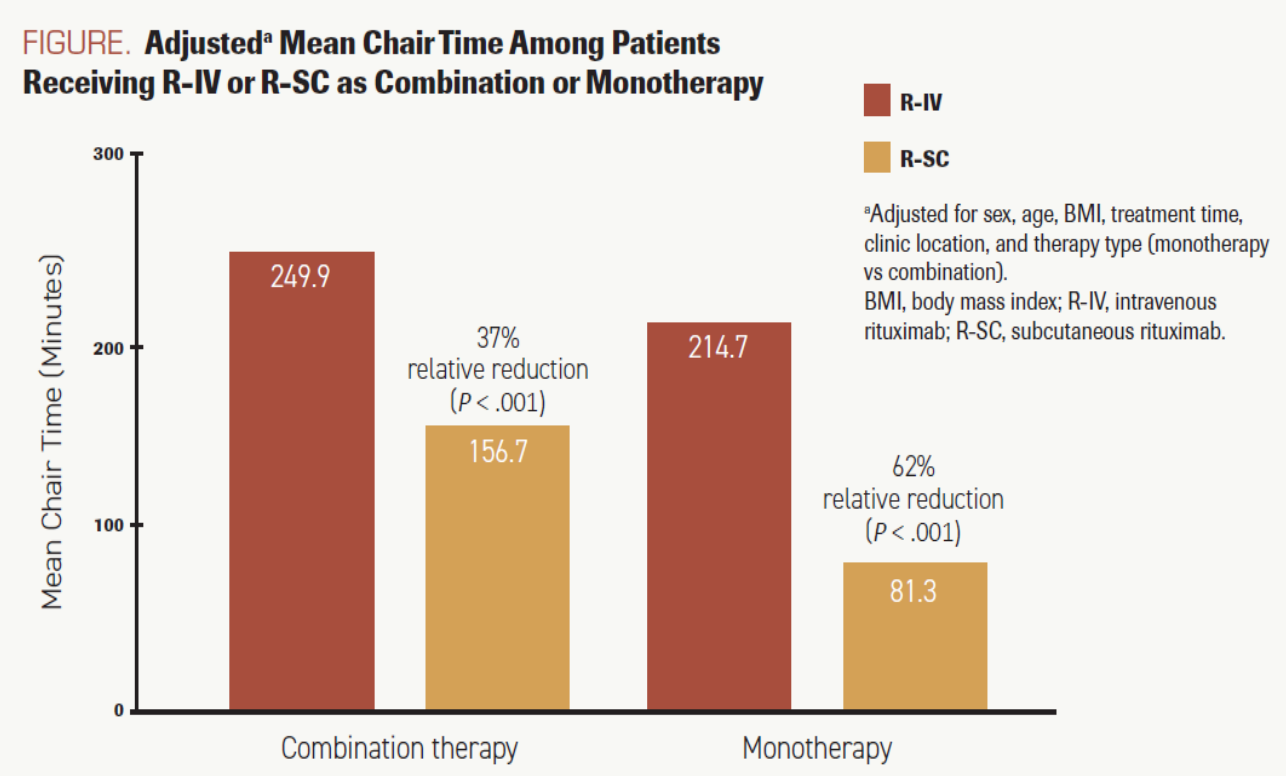
Product	Dose	Volume
Herceptin Hylecta (trastuzumab) - Roche	600 mg	5 mL
Rituxan Hycela/ Mabthera (rituximab) - Roche	1400 mg	11.7 mL
Darzalex FASPRO (daratumumab) - Janssen	1800 mg	15 mL
Phesgo (pertuzumab & trastuzumab) - Roche	600 / 1200 mg	10 / 15 mL

* Marschall, Christoph, et al. "Drug Product Characterization of High Concentration Non-Aqueous Protein Powder Suspensions." Journal of Pharmaceutical Sciences 112.1 (2023): 61-75.

Patient Care and practice efficiency with Rituximab SC

SC administration is associated with reduced oncology chair time and improved clinical practices while reducing the burden on healthcare resources*

Chair time has a significant impact for patient and clinical practices in oncology



- From the perspective of clinical workflow, Rituximab-SC adoption resulted in ***substantial time savings*** for both the patient and health system.
- Rituximab-SC which may ***improve practice efficiency*** and allow more patients to be treated.
- Reduced chair time would be expected to translate into reduced time in the infusion suite with associated ***improvement in convenience and patient burden***.

* Drill, E. et al. (2021). Real-World Assessment of Patient Care and Practice Efficiency With the Introduction of Subcutaneous Rituximab. Oncology, 35(12).

Subcutaneous IgSC by pump or rapid push infusion

Multi-center, open-label, randomized, crossover, noninferiority trial in adult Primary Immunodeficiency (PID) with IgSC 165 mg/mL (Gammanorm®) over two consecutive 3-month periods using pump and rapid push*

Rapid push proved to be an efficacious and cost-effective alternative to pumps adding to patient choice and increasing flexibility during long-term Ig replacement therapy

- Dose: ***0.4-0.8 g/kg (2.5-5 mL/kg) monthly*** - administered at repeated intervals (from Q1W to every other day).
- Pump infusions:
  - Volume / injection site: <25 mL (first 10 infusions) and then gradually increase to ***up to 35 mL***, if tolerated.
  - Flow rates: 15 mL/h/site (first infusions) and gradually increase ***up to 25 mL/h/site (0.41 mL/min)*** as tolerated
- Rapid manual push infusion
  - Volume (single infusion site) ***<25 mL***
  - Flow rate: ***1–2 mL/min*** (60-120 mL/h/site).
- After on-site training, self-administered at home.

QoL and other psychometric outcomes

		Rapid push	Pump
LQI	I: Interference	78.9 [74.7–83.2]	84.3 [79.8–89.1]
	II: therapy-related problems	73.5 [67.8–79.7]	73.7 [67.8–80.1]
	III: therapy setting	87.7 [82.8–92.8]	87.0 [82.1–92.2]
TSQM	Satisfaction with treatment	76.8 [70.6–83.6]	75.9 [69.8–82.6]
PRISM	Burden of disease	9.4 [6.2–14.3]	8.2 [5.3–12.6]
	Burden of device	7.9 [5.5–11.4]	9.3 [6.4–13.6]

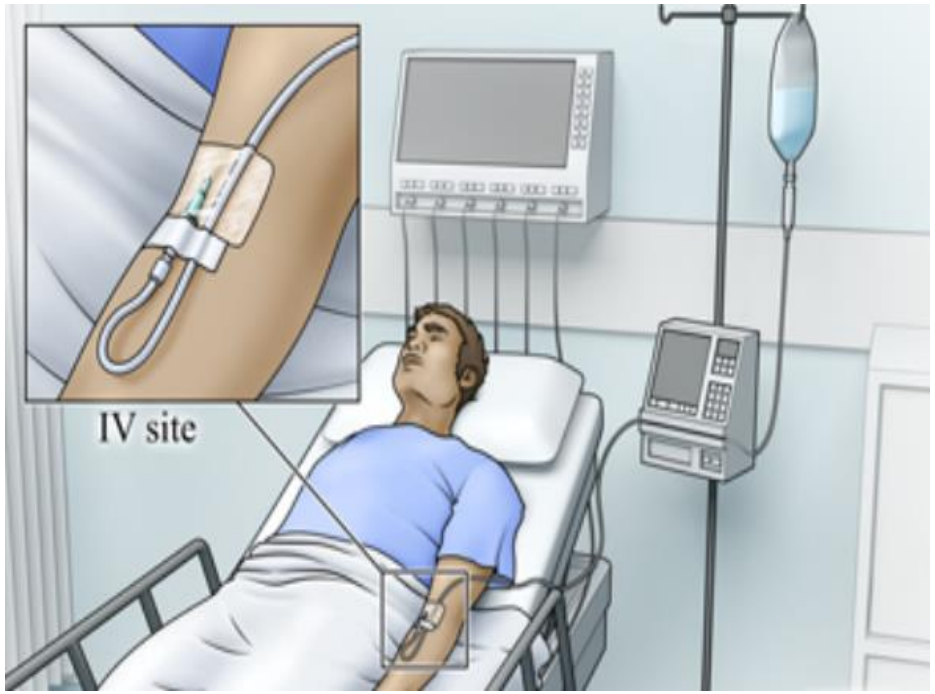
QoL: quality of life – LQI: life quality index – TSQM: treatment satisfaction questionnaire for medication – PRISM: pictorial representation of illness and self-measure

* Warnatz, K. et al. (2022). Subcutaneous Gammanorm® by pump or rapid push infusion: Impact of the device on quality of life in adult patients with primary immunodeficiencies. Clinical Immunology, 236, 108938.

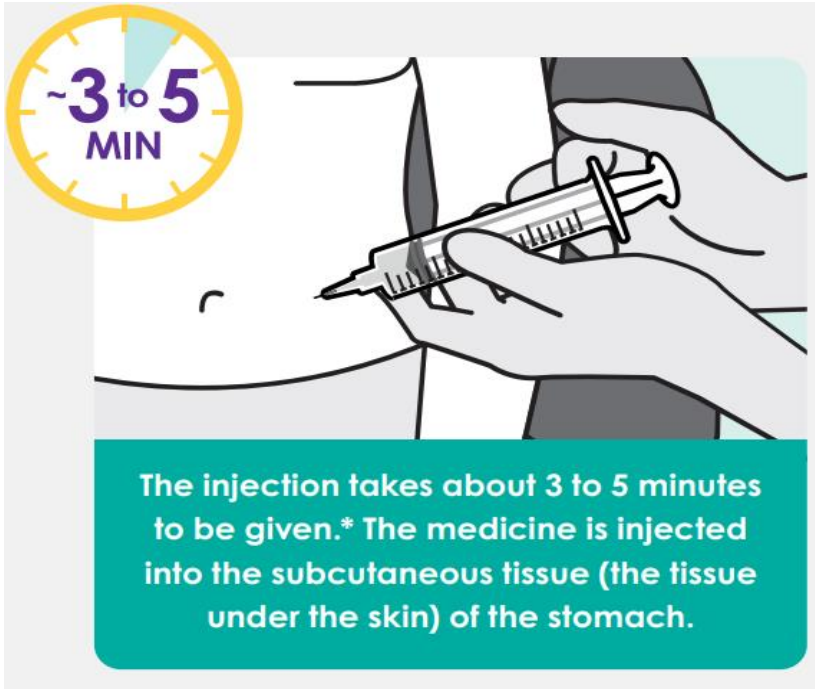
Outstanding Darzalex FASPRO for Multiple myeloma

Self-explanatory figures!

- Switch from **IV to SC is 85% complete** in the US
- Sales for **H1-2022 hited $3.8 billion***



Infusion in 3 to 5 hours



15mL SC infusion with manual syringe injection

* Fierce Pharma, July 26, 2022

Conclusions

- **CMC workflows have been accelerated to enable speed to clinic during the COVID period with a remarkable strengthening of platform development**
  - ➜ from DNA to IND/IMPD 10-15 months
- **Formulation platforms are commonly deployed for early clinical stages (FIH) and phase 1 extension studies**
- **The transition to SC administration is a strong trend for biotherapeutics supported by innovation combining formulation and device**

THANK YOU