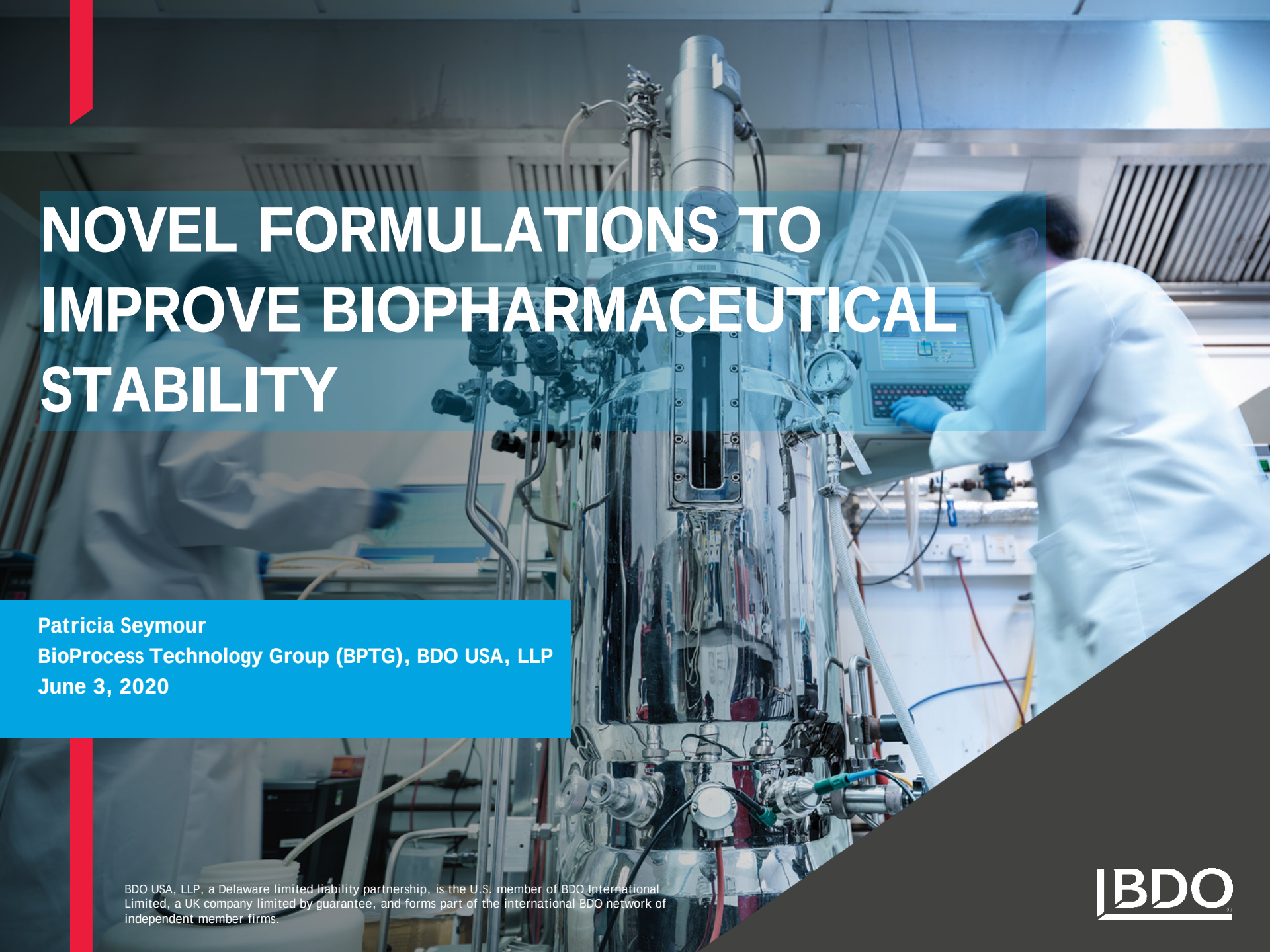

NOVEL FORMULATIONS TO IMPROVE BIOPHARMACEUTICAL STABILITY

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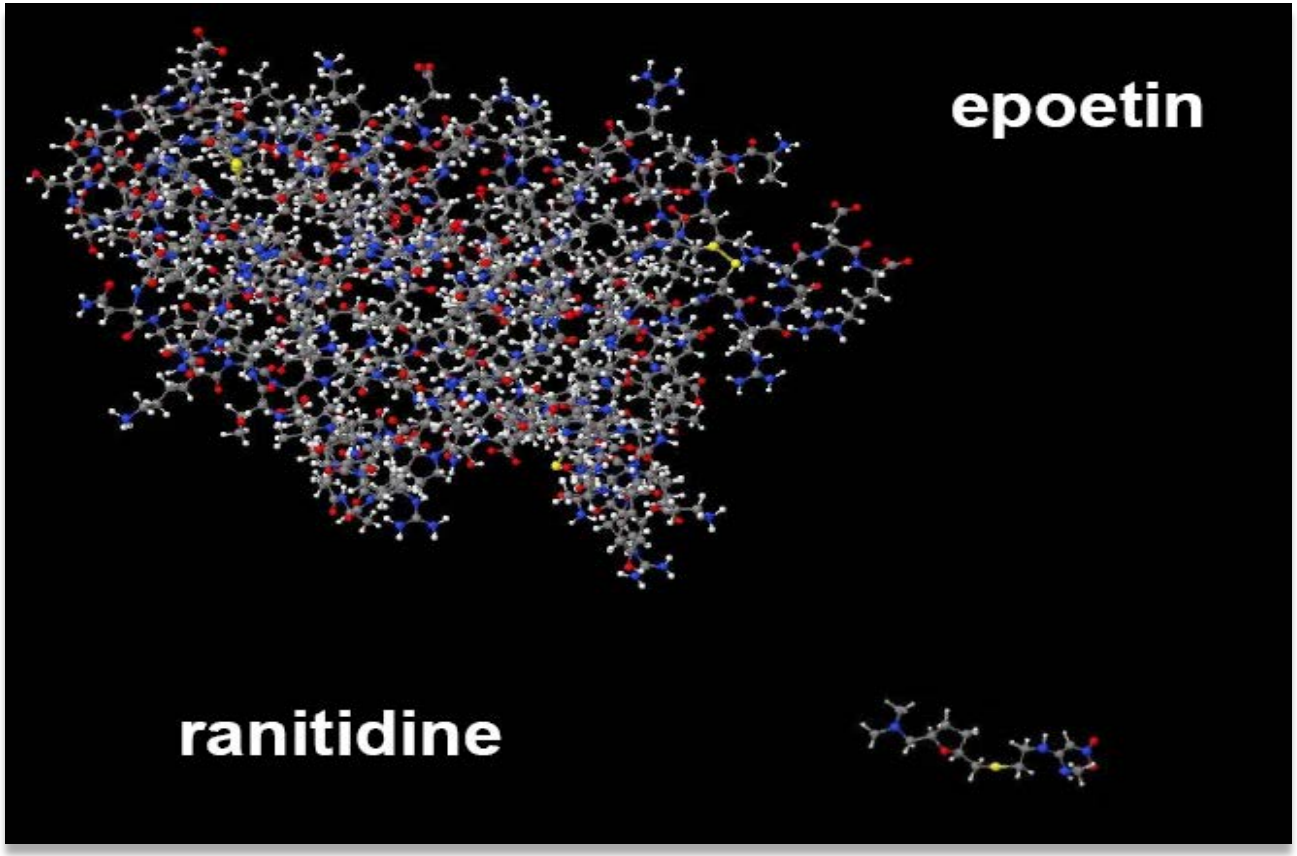
BDO

Introduction

- What is unique about biopharmaceuticals and their formulation requirements
- How can novel excipients improve biopharmaceuticals stability



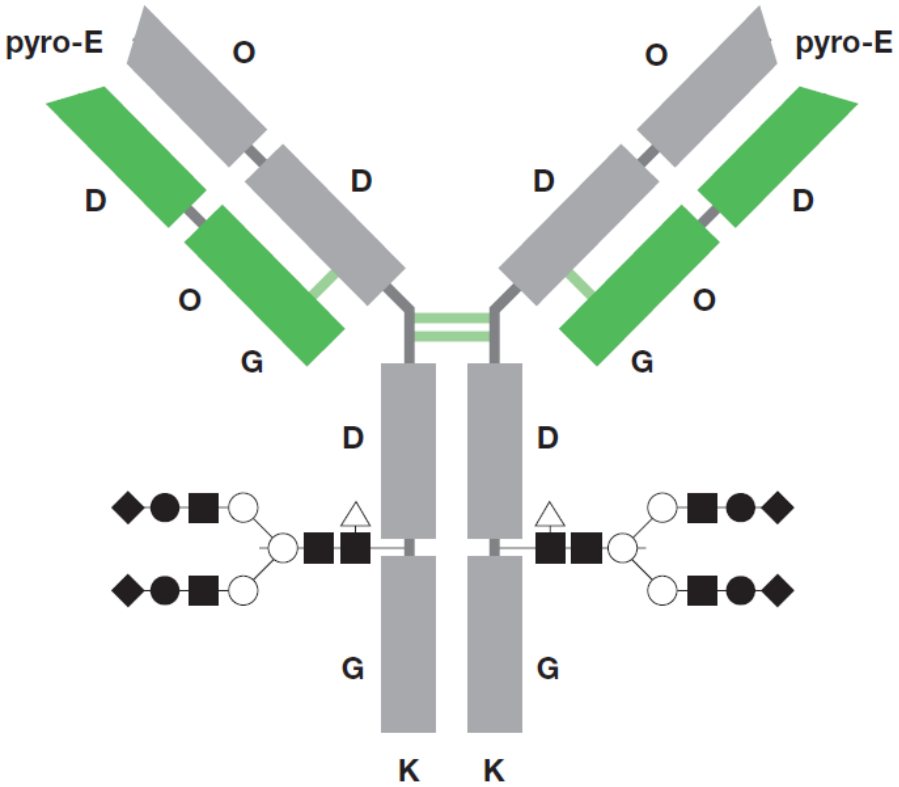
CMC Development – Large (Biopharmaceuticals) and Small Molecule Drugs

- CMC development of a small molecule drug and a biopharmaceutical share the common objective:
  - Deliver *regulatory* approvable processes that produce quality product at an acceptable COGS in a manufacturing setting
- Technical and Regulatory challenges are different due to:
  - Recombinant organism
  - Size and complexity of the molecules
  - Intrinsic heterogeneity in a biopharmaceutical
  - Biological activity of biopharmaceutical products resides in higher order structure
  - Nature of impurities – both process and product related
  - Number and modes of analytical methods used to characterize and release drug
  - More complex scale-up from pilot plant to commercial scale
  - Stringent microbiological control required as process streams are predominantly aqueous
  - Limited formulation options (currently)
  - Biopharmaceuticals are predominantly injectables that cannot be terminally sterilized requiring significant investment in aseptic filling facilities and capabilities

Advantages and Limitations of Biopharmaceuticals

Advantages	Limitations
o Rapid approach to therapeutic development for new targets	o Limited ability to address intracellular targets
o Proven success in treatment of an increasing range of indications	o Parenteral administration nearly universal
o Structural complexity -> highly specific functional activity	o Structural complexity -> PD/AD expensive and time-consuming
o Human proteins generally well tolerated	o Process changes and product characterization more expensive
o Monoclonal antibodies (a subset of biopharma) can leverage “platform” capabilities	o Potentially immunogenic
o Substantial and expanding capability to analyze, develop and manufacture	o Require cold chain for supply chain and distribution
o Few biopharmaceuticals fail due to safety issues (Phase 1)	o Bulk drug costs high ($/kg basis)
o Low material requirements for early clinical studies (~1 kg for FIH studies)	o Large-scale manufacturing capital intensive

mAb Simplified Structure



pyro-E	Pyro-Glu (2)
D	Deamidation (3 × 2)
O	Methionine oxidation (2 × 2)
G	Glycation (2 × 2)
	High mannose, G0, G1, G1, G2 (5)
	Sialylation (5)
K	C-term Lys (2)

2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600
$(9600)^2 \approx 10^8$ Variants

Kozlowski S, Swan P. Current and future issues in the manufacturing and development of monoclonal antibodies. Adv Drug Delivery Rev. 2006 Nov;58(5-6):707-22.

Degradation Pathways

Types of Degradation	Susceptible Amino Acid	Suitable Analytical Methodology
Oxidation	Methionine, some tryptophan and histidine	Reverse phase HPLC, Peptide mapping
Deamidation	Asparagine, some glutamine	Ion exchange HPLC, Isoelectric focusing (IEF), Quantitative assay of isoaspartic acid
Disulfide bond rearrangement	Cysteine and cystine	Peptide mapping, Quantitative analysis of free sulfhydryl groups
B elimination with rearrangement	Aspartic acid	Peptide mapping
Hydrolysis	Aspartic acid	Size exclusion (SEC) HPLC, SDS-PAGE, Mass spectrometry (MS)
Cross linking	Cysteine, some lysine and glutamic acid	SDS-PAGE, SEC HPLC, Multi-angle light scattering (MALS), Analytical ultracentrifugation (AUC), MS
Loss of tertiary structure	N/A	Circular dichroism (CD), Fourier transform infrared spectroscopy (FTIR), Intrinsic and extrinsic tryptophan fluorescence, Potency
Aggregation	N/A	SDS-PAGE, SEC HPLC, MALS, AUC, MS
Precipitation	N/A	Visual observation, MALS, AUC
Adsorption	N/A	Protein Concentration, Surface Extraction

Immunogenicity

- Proteins, even naturally produced proteins, can provoke an immune response
- Analogous to genotoxicity concerns with small molecules
- Antibody formation can
  - Alter biological availability
  - Alter efficacy
  - Result in life threatening responses, i.e. anaphylaxis
- Impacted by both patient, product and process related factors
  - Disease state and immune status
  - Dose and frequency of dosing
  - Cell line and raw materials
  - Can be affected by changes to the product or the process
- Increased regulatory concerns, especially about aggregation and subvisible particulates
- Immunogenicity must be monitored during clinical development

Excipients Used in Biopharmaceutical Formulations

- Growing need for excipients that are
  - Fit-for-purpose of formulating, manufacturing, and delivering the new generation of biopharmaceuticals
- Excipients should meet the appropriate compendial standards whenever possible – **global harmonization is critical.**
  - FDA Inactive Ingredient Database (IID)
  - International Pharmaceutical Excipient Council (IPEC)

Configurations and Commercial Products by Formulation from bioTRAK®

- Number of buffers/excipients in a combination ranged from 1 to 13 components
  - Average of 4 components
- 5 Most common components
  - Sodium Chloride used in 101 formulations
  - Polysorbate 80 used in 86 formulations
  - Sodium Phosphate, used in 77 formulations
  - Sucrose used in 76 formulations
  - Mannitol used in 57 formulations
- 35 Components are used in a single formulation, examples include
  - Alanine, lyophilized enzyme
  - Cinnamic Acid, liquid enzyme conjugate
  - Dextran 40, lyophilized antibody conjugate
  - Nicotinamide, liquid hormone

Configurations and Commercial Products by API Concentration

Concentration[a] (mg/mL)	No. Configurations[b]	No. Products[c]	% of Antibody Products[d]
<1 mg/mL	320	99	5%
1-25 mg/mL	234	135	45%
26-100 mg/mL	72	45	96%
>100 mg/mL	34	20	96%

[a] For lyophilized products, concentration after reconstitution with appropriate diluent according to package insert

[b] Configurations based on individual API concentration, format, container and formulation

[c] No. Products represent the unique number of products represented in a given set of parameters. In some cases, a product may be represented in more than 1 category.

[d] Percent of products within a given set of parameters which are antibody products to include: Full-length MAbs, including bispecific, biosimilar, named and conjugates as well as antibody fusion proteins

Configurations and Commercial Products by Format

Format	No. Products	% of Antibody Products
Liquid	168	46%
Lyophilized	99	34%
Both	14	57%

Configurations and Products by Container

Container	No. Configurations[a]	No. Products	% of Antibody Products[b]
Autoinjector	6	5	80%
Cartridge	39	24	-
PF Pen	104	54	31%
PFS	147	75	49%
Tube	1	1	-
Vial	363	208	47%

[a] *Configurations based on individual API concentration, format, container and formulation*

[b] *Percent of products within a given set of parameters which are antibody products to include: Full-length MAbs, including bispecific, biosimilar, named and conjugates as well as antibody fusion proteins*

Novel Excipients in Formulations

- A novel excipient is one that has never been used and "reviewed in an FDA approved drug product or does not have an established use in foods".
  - FDA has not reviewed the safety of novel excipients outside the context of an IND, a new drug application (NDA), or a biologics license application (BLA) describing a finished product to which the excipient has been added.
- Applicants are hesitant to use novel excipients
  - How much is safe?
  - In long term or chronic use, how long can safety be assured?
  - Will the excipient create an unintended consequence under approved conditions of use?
- FDA is interest in establishing a program to review the toxicology studies independent of the IND, NDA, and BLA process to evaluate "the safety of the novel excipient at anticipated levels and duration of exposure, by anticipated routes of administration."

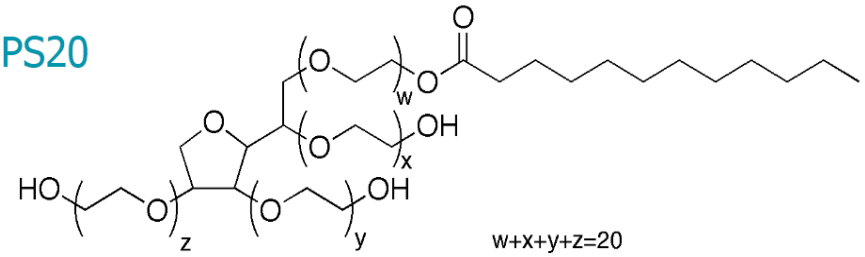
Target Areas for Novel Excipients in Formulations for Biopharmaceutical Products

- New stabilizers/surfactants to improve solubility, where polysorbates present stability liabilities, and agents to prevent aggregation and instability
- Oral delivery of peptides, such as protease inhibitors and permeation enhancers
- Intra-nasal delivery of peptides and other poorly permeable compounds
- Enablement of oligonucleotide, gene- and cell-based therapies
- Amino acids to improve solubility, stability, and effectively reduce viscosity
- Biodegradable polymers, which can facilitate fabrication of novel systems and modulation of drug release, and
- Hydrophobic salts that have the potential to “dramatically reduce” viscosity of highly concentrated antibody formulations.

Biopharmaceutical Formulation Challenges

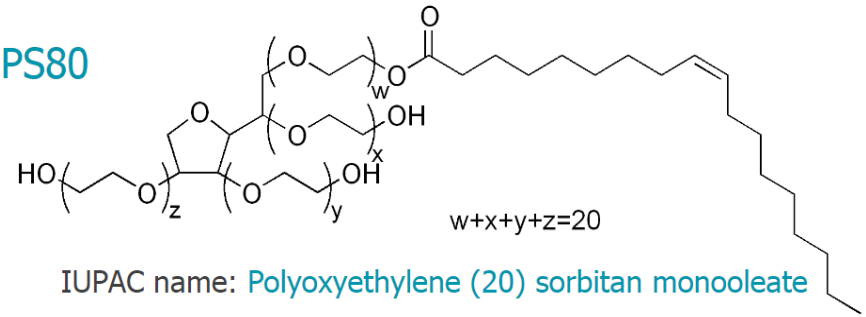
- Need to stabilize antibodies from interfacial stresses in liquid formulations
  - Achieving adequate shelf life and agitation stability of biologics can be difficult with compendial surfactant excipients due to oxidation risks of both the excipient and protein, interfacial activity of complex therapeutic proteins, and hydrolysis of the excipient.

PS20



IUPAC name: Polyoxyethylene (20) sorbitan monolaurate

PS80

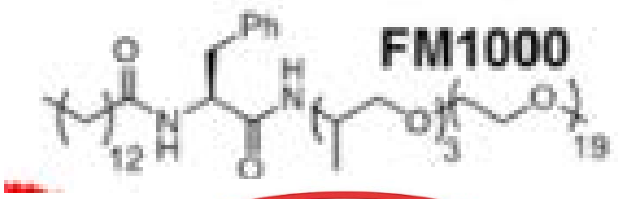


IUPAC name: Polyoxyethylene (20) sorbitan monooleate

Hawe A. Bioprocess Summit, Cambridge, MA 2018

Biopharmaceutical Formulation Challenges

- Need to stabilize antibodies from interfacial stresses in liquid formulations
  - Novel surfactants that stabilize proteins from degradation at air-water and solid-water interfaces during manufacturing, shipping, and over the course of the shelf life in the presence of residual host cell proteins/enzymes would greatly benefit the development of robust biologic formulations.
  - Have significant public health benefits by decreasing protein aggregation and particle formation in liquid biologic formulations, thereby increasing shelf life.



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Biopharmaceutical Formulation Challenges

- Formulation at high concentrations
  - High concentration formulations for subcutaneous injection
- Several challenges with high concentration formulations
  - Viscosity and protein instability
  - Small injection volumes
  - Influence on delivery of the interplay between the extracellular matrix (ECM) and the protein characteristics of a biologic drug,
  - Impact on the pharmacokinetics (PK) of a biologic drug when moving from IV to SC,
  - Potential for increased immunogenicity in SC vs. IV formulations.

The trastuzumab and hyaluronidase-oysk combination is a ready-to-use formulation that can be administered in 2 to 5 minutes, compared to 30 to 90 minutes for intravenous trastuzumab.

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

Herceptin HYLECTA™
trastuzumab and hyaluronidase-oysk
INJECTION FOR SUBCUTANEOUS USE | 600 mg/10,000 units

Further Consideration

- Incentives
  - Low volume requirements for excipients for biopharmaceutical could be a barrier to entry for some novel excipient manufacturers
  - Market exclusivity for the development of novel excipients could further incentivize their development
  - Concomitant development of a USP/NF monograph during the novel excipient review process, as there is currently a delay between when an excipient is listed in the IID and publication of the USP/NF monograph
- Data disclosure
  - If FDA's review results in the material being listed in the IID, publication of the reviews would increase the potential for multiple pharma company use
  - Excipient supplier grant access in a manner similar to how access is granted to DMFs

THANK YOU!

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