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Formulation and Stabilization of Biotherapeutics
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Formulation of Biotherapeutics: Introduction

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July 21-23, 2014

M.I.T.

Course Goals

- Appreciate the importance of formulation development in bringing a biopharmaceutical product to market
- Identify the primary aspects of stabilization of proteins against physical instability (e.g., aggregation)
- Learn about the primary mechanisms of chemical degradation
- Understand the mechanisms of aggregation and the impact on kinetic profiles

Course Goals

- Examine the analytical methods employed to detect and quantify the levels of soluble aggregates and subvisible particles in protein products
- Use these mechanistic insights to develop liquid, frozen, and lyophilized dosage forms of proteins in a rational and defensible manner
- Learn about some important nuances for stabilization of peptides, vaccines, ADCs, and PEGylated proteins

Role of Formulation in Drug Development

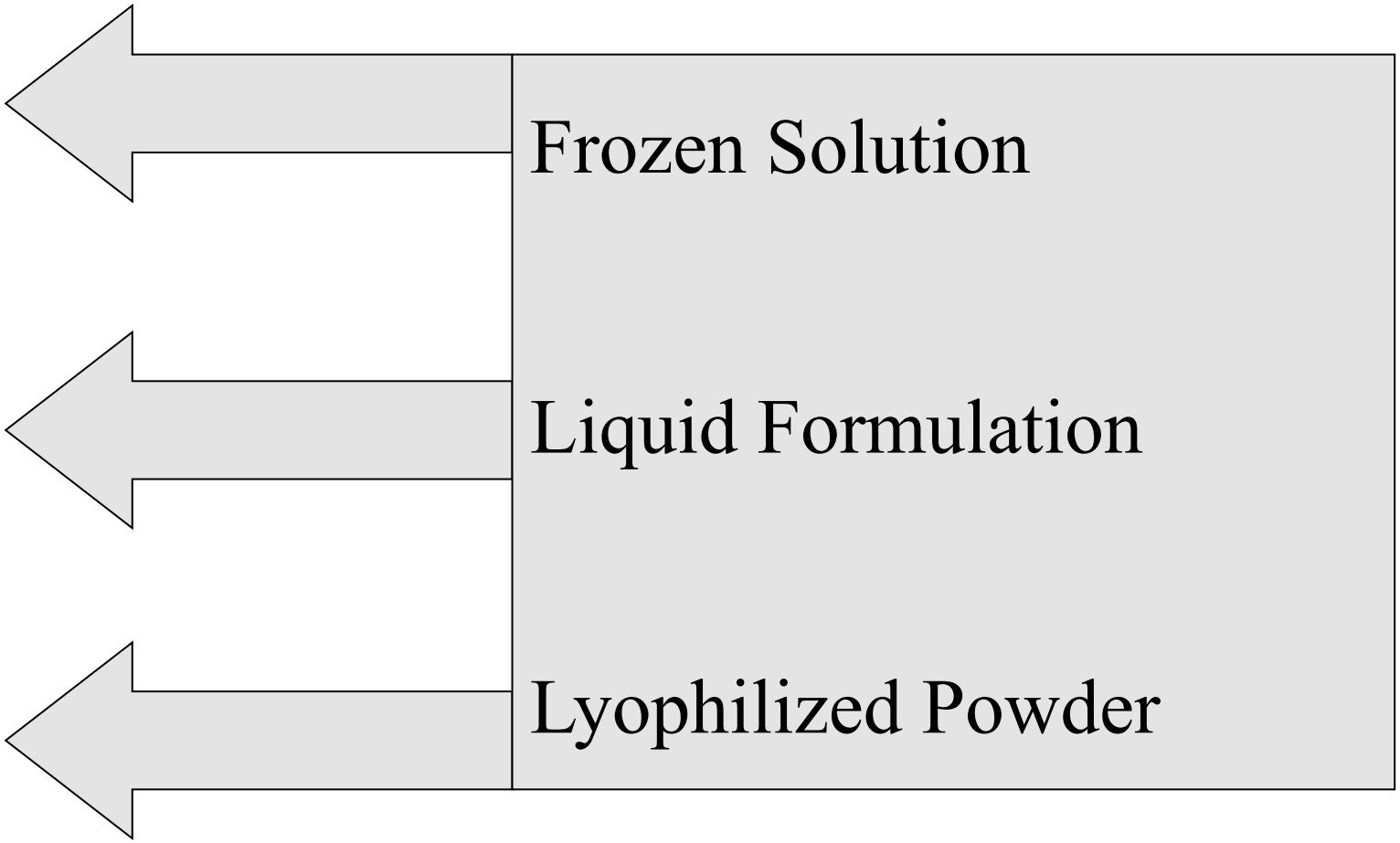
- **To ensure optimal product 'performance' by the appropriate choice of (i) dosage form, (ii) excipients, (iii) process and (iv) packaging**
- The latter are done in collaboration with other groups
- What is 'performance'?

  Quality as measured by stability, solubility, potency, safety, etc.

Formulation Goals

- Develop a formulation strategy
- Obtain and meet the target profile
- Select dosage form
- Make excipient choices
- Assay development
- Employ accelerated stress testing/Select conditions
- IP constraints/goals
- Determine compatibility of formulation and container
- Ensure process and formulation are compatible

Three Primary Dosage Forms



Hallmark of a Good Formulation

- Simple (that's why good formulations look easy)
- Manufacturing-friendly
- Safe (use appropriate excipients)
- Meets shelf-life objectives
- Satisfies target profile
- Meets time lines
- May involve 'informed compromise'
- Must be rational/defensible

Two Types of Protein Instability

CHEMICAL

- Deamidation
- Asp-isoAsp Interconversion (Asp Isomerization)
- Racemization/Epimerization
- Proteolysis
- Trp Hydrolysis
- Hinge Region Hydrolysis
- Beta-elimination
- Oxidation

PHYSICAL

- Denaturation
- Aggregation
- Precipitation
- Surface Adsorption

- Disulfide Exchange
- DKP Formation
- Condensation Reactions
- pGlu Formation

Manning et al., *Pharm. Res.* **2010**, 27: 544-575

Differences of Proteins from Small Molecules

1. Proteins are multi-functional
2. Most proteins adopt a globular structure that is essential for activity
3. Molecular weight differences
4. Numerous chiral centers in proteins
5. Unique pH response for each protein
6. Proteins are immunogenic

Considerations for Liquid Formulations

- Increased desirability for marketing
- Chemical stability is harder to control
- Excipients may include excluded solutes, surfactants, buffers, chemical stabilizers, others
- Damage due to agitation is a potential issue for transport and handling
- Need to evaluate F/T stability
- Higher protein concentration formulations raise additional issues

Important Aspects of Physical Stability

- Conformational Stability

  Is the 3-D structure maintained?

- Colloidal Stability

  How strong are protein-protein interactions?

- Interfacial Stability

  Does exposure to interfaces cause damage?

Considerations for Lyo Formulations

- Physical stability is better (less aggregation)
- Chemical stability is easier to control (no water)
- Excipients may include lyo protectants, buffers, bulking agents, sometimes others
- Room temperature stable product is possible
- No worry about agitation-induced damage during shipping
- Higher protein concentration formulations raise additional issues

Importance of Analytical Methods

- All formulation development is assay limited
- Structural tools are essential for proper development of protein formulations (but have limitations)
- HPLC is still the centerpiece of stability testing (RP, SEC, IEX)
- Different analytical methods are needed for liquid development vs. dried formulations
- ***Critical issue is knowing which method is needed for each purpose or need***