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Formulating Biologic Drugs for Subcutaneous Administration: Challenges and Excipient Solutions

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Outline

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  - Formulations used to administer biologic drugs
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- Regulatory (clinical) requirements to support formulation changes

The Biotherapeutics Industry

- Since the marketing of the first biologic, human insulin, in the 1980s, biologics have become one of the fastest growing classes of therapeutic compounds used in the clinic, and in development.

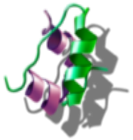
- The development of new treatment modalities in emerging areas such as cell and gene therapies, continue to revolutionise the medical landscape.

- Biologics, however, are different from conventional medicines (pharmaceuticals) in that they are large, complex protein molecules and are inherently more variable, resulting in more challenges in their manufacture and delivery to patients.

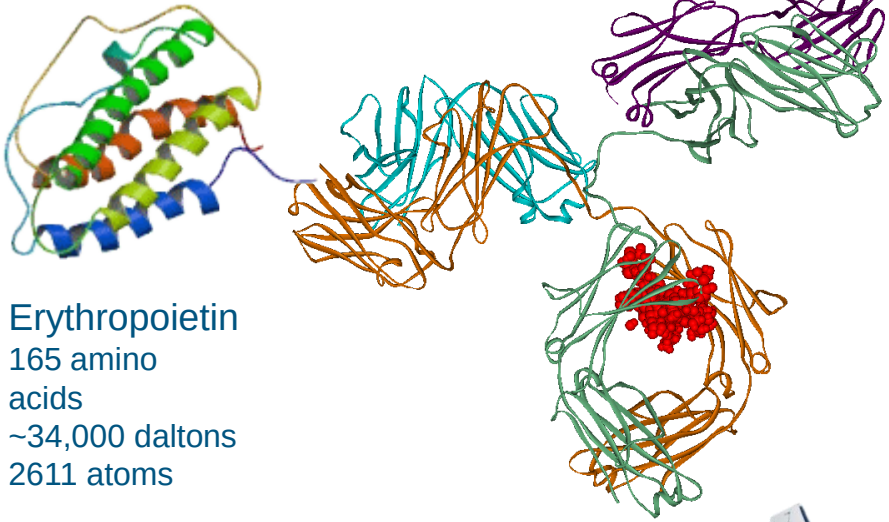
Small Molecule

Biologics

Acetyl-salicylic acid
~180 daltons
21 atoms



Insulin
51 amino acids
~5,800 daltons
788 atoms



Erythropoietin
165 amino acids
~34,000 daltons
2611 atoms

IgG1 antibody
~1300 amino acids
~150,000 daltons
>20,000 atoms

Gene and cell therapies

Pharmaceuticals vs. Biologic Drugs

	Pharmaceuticals	Biologic Drugs
Size	Small, low molecular weight	Large, high molecular weight
Structure	Simple, independent of manufacturing process	Complex (heterogeneous), defined by manufacturing process
Modification	Well defined	Many options
Manufacturing	Chemically synthesized	Produced in living cells and each cell line is unique
Characterisation	Simple to characterise	Multiple complex assays to completely characterise
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	Immunogenic

Modes of Administering Biologic Drugs

- Due to the limited chemical stability and gastrointestinal degradation of proteins, biologic drugs are generally administered by the parenteral route such as intravenous (IV), subcutaneous (SC) or intramuscular (IM).
- There is an increasing trend, however, in the development of biologic products to be delivered by the **SC route,** as it may offer an alternate route that is cheaper and more convenient to administer.
- Despite the benefits of SC routes, it is not without complications mainly due to formulation issues, impacts on bioavailability and immunogenicity.

Challenges Associated with SC delivery

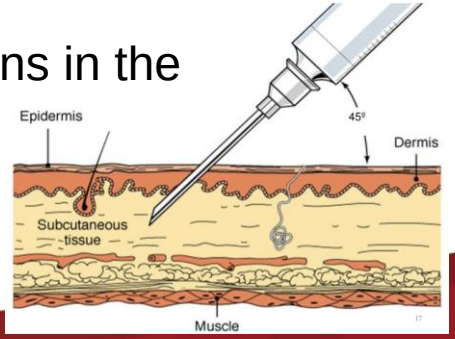
- **Small Injection Volumes** are employed with SC routes (vs. IV infusions) and thus requiring SC formulations to be comprised of higher concentrations of protein.

  - Higher protein concentrations can cause protein crowding and increase the risk of aggregation due to protein-protein interaction

  - Aggregation interferes with protein absorption and can increase risk of immunogenicity

  - Potential safety concerns due to a higher dose of biologic drug being delivered

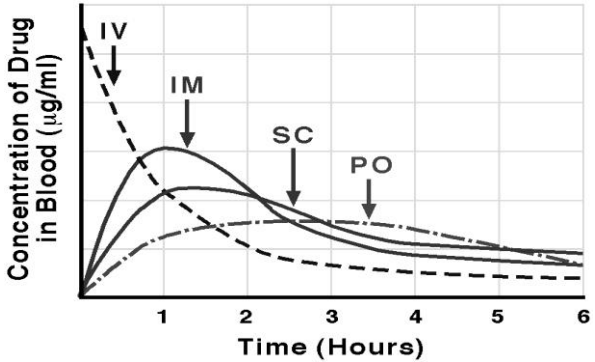
- The interplay between the **Extracellular Matrix (ECM)** and the protein characteristics of a biologic drug influences delivery.
  - The SC space limits injection volume
  - Pre-systemic protein degradation decreases drug available for absorption
  - The ECM has a complex physiology and can be a significant barrier to effective delivery (e.g., excessive adipose tissue in obese subjects)
  - Potential for immunogenicity due to aggregation of proteins in the ECM
  - Immunogenicity, in turn, can impact clinical performance (pharmacokinetics, safety and efficacy)



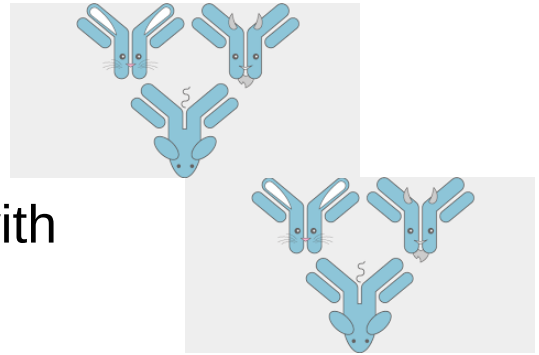
- **The pharmacokinetics (PK)** of a biologic drug are impacted when moving from an IV to a SC route of administration

  - Decreased bioavailability due to the SC space having few blood vessels for absorption

  - Prolonged exposures / decreased clearance (potentially due to immunogenicity)

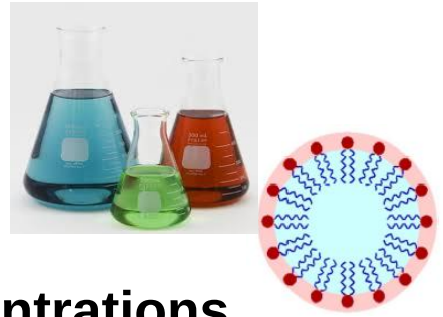


  - Lymphatic uptake from the interstitial space plays a key role for larger proteins.



- **Increased immunogenicity** has been suggested with SC formulations as compared to IV formulations.
- Increased immunogenicity may be attributed to formulation differences such as higher protein concentration, the potential for aggregation as well as the potential for excipients to elicit immunogenicity.
- The clinical impact of immunogenicity requires consideration when developing SC formulations.

Formulation Considerations for SC Delivery of Biologic Drugs



- **To address issues relating to high protein concentrations**
  - Stabilisers to reduce aggregation and denaturing
  - Buffer screening
  - Evaluate protein colloidal stability to assess aggregation patterns and unfolding characteristics
  - Use of surfactants to reduce protein-protein interaction (e.g., polysorbate-20 and 80)
  - Salt solutions (e.g., NaCl) offer stability

- The **biophysical characteristics of a protein drug molecule** itself also influences the PK and hence drug delivery.

  - Molecular weight – restrictions in the SC space limit absorption of large molecular weight proteins

  - Molecular charge (pH and isoelectric point) – potential influence on the stability and performance of the protein from its stable formulation to media within the ECM

  - FcRn binding capacity – Fc variants of monoclonal antibodies may bind with different affinity to FcRn and influence bioavailability

Excipients are an integral part of biotherapeutic products

- Enhance solubility of the active protein
- Enhance process and shelf life stability of the active protein
- Control pH and tonicity
- Maintain preferred stable conformation of proteins including exposure of the functional epitopes
- Prevent aggregation or degradation of the active protein
- Include bulking agents, antioxidants, or preservatives

- **To enhance delivery, formulation excipients and additives may be used such as:**

  - Hypertonic solutions to increase lymphatic uptake by altering the osmotic pressure of an injected biologic drug

  - Tonicity agents e.g., O-phospho-L-serine (OPLS) and mannitol

Hyaluronidase

- Hyaluronidase is an additive that can increase SC absorption of proteins by degrading the ECM while preventing nonspecific binding by the administered protein
- Hyaluronidase catalyzes the hydrolysis of the hyaluronic acid component of the ECM. This lowers the viscosity of hyaluronan and increases tissue permeability by destabilising the fibrinogenous network
- The effects of hyaluronidase are safe and reversible

- Recombinant human hyaluronidase has been used in a number of biologic products for SC administration
- The following SC products have been recently approved in Canada that employ recombinant human hyaluronidase to facilitate SC delivery
  - Rituxan SC (rituximab)
  - Herceptin HC (trastuzumab)
- The clinical success of these products may evolve into a new formulation for future SC products.

Regulatory Considerations for Formulation Changes

- In Canada, the data requirements to support changes in formulation are outlined in the Health Canada Guidance Document *Post-Notice of Compliance (NOC) Changes: Quality Document*

https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document/quality-document.pdf

Clinical Requirements to Support Formulation Changes

- Comparative *in vivo* clinical studies (designed as equivalence studies) should be submitted to demonstrate:
  - ➢ Comparable PK characteristics (AUCt and Cmax)
    Note: Clearance parameters should be also compared and reported
  - ➢ A comparable safety and immunogenicity profile
  - ➢ A justification should be provided for the choice of the study population used in the equivalence study (i.e., is it a sensitive population?)

Clinical Requirements to Support a SC Formulation as an Alternative to an IV Formulation

- Comparative *in vivo* clinical studies (designed as non-inferiority studies) should be submitted to demonstrate:
  - Non-inferior PK characteristics (based on Ctrough) of the SC formulation as compared to the IV formulation.
  - A comparable safety and immunogenicity profile.
  - Comparable efficacy. A justification should be provided for the choice of the study population and the relevancy of the efficacy endpoints evaluated if the studied population is different to the indicated patient population.

Granting of Indications

- Many biologic drugs are authorised for more than one indication.
- When changes are made to the formulation of a marketed biologic drug or, if a new route of administration is proposed, Health Canada does not automatically grant the use of the new formulation or new route of administration to all authorised indications.
- Sufficient scientific evidence or rationale should be provided in order to claim all authorised indications.

In Conclusion:

SC administration of biologic drugs offers several potential advantages over the other routes of administration, for example, IV infusion.

Through understanding of absorption kinetics after SC administration, it is anticipated that additional new excipients will be developed by biotherapeutic companies to address current challenges with the development of SC formulations for biologic drugs.

While the race to develop new SC dosage forms continues, the biotherapeutic industry should be reminded that they need to meet the Canadian Regulatory requirements in demonstrating that the new formulations are of high quality, safe, effective and do not pose additional risks to Canadians.

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