The delivery and safety of biologics

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 101007939. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies.

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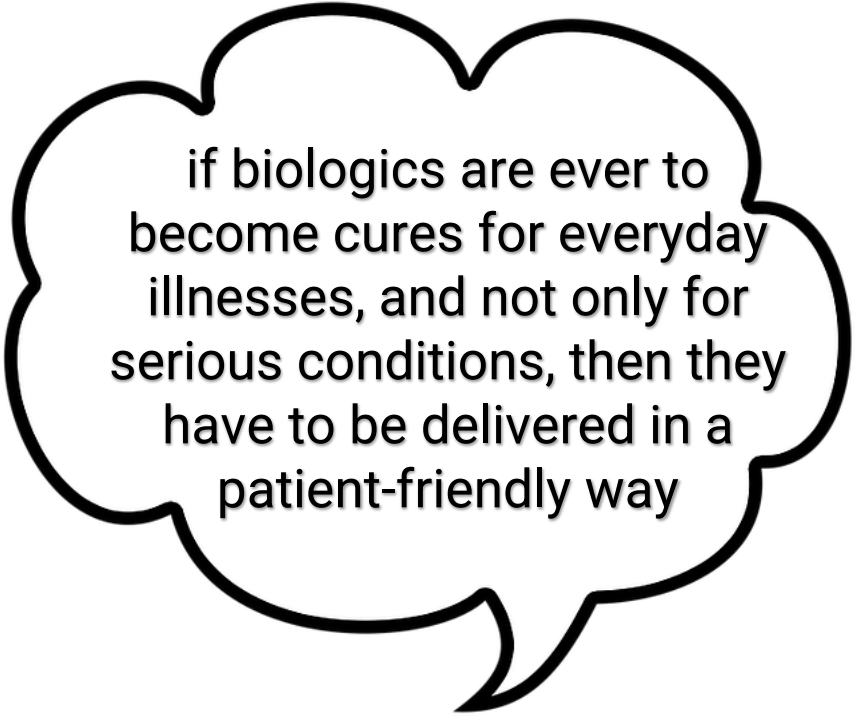
Challenges in delivery of biologics

- Low bioavailability
  - Poor transport over biological barriers
  - Rapid clearance and in vivo degradation

Complicated, intrusive delivery

- Needles
- Need for assistance by medical professionals



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Low uptake through oral delivery

Degraded in the GI tract due to;

- Acidic environment
- Enzymes
  - Proteases and peptidases
  - Nucleases

Low passage over the epithelial barriers

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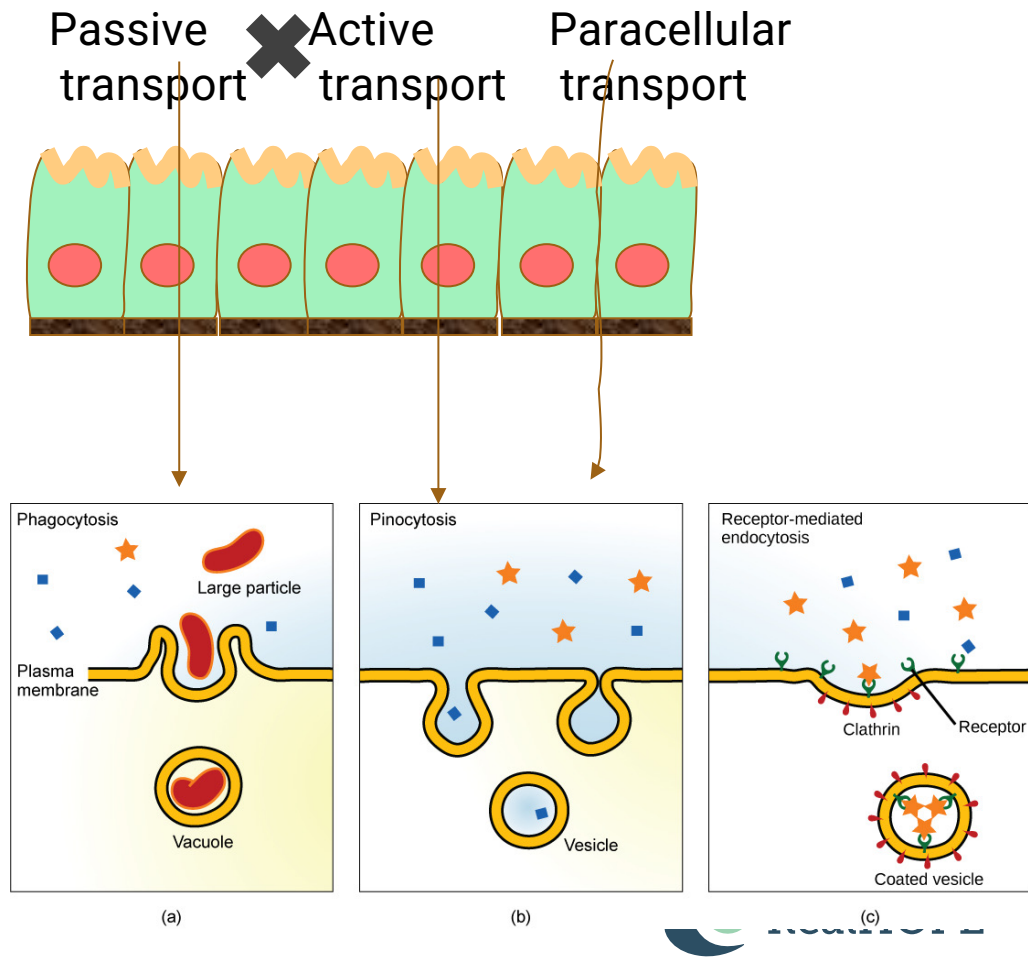
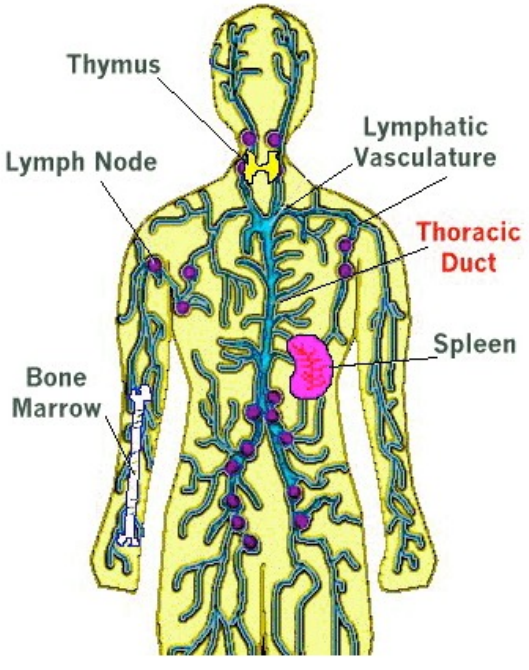
Low uptake through epithelial cells

- No passive transport through cell membranes
- Difficult but possible transported through paracellular transport via the tight junctions
- Active transport and receptor mediated transport
- Uptake through endocytosis:
  - Phagocytoses for particles or viruses
  - Pinocytosis
  - Receptor mediated endocytosis



Lymphatic uptake

- Uptake into the lymphatic system
- Important for oral vaccines
- Advanatges
  - Bypassing first-pass metabolism
  - Prolonged circulation
  - Reduced systemic exposure



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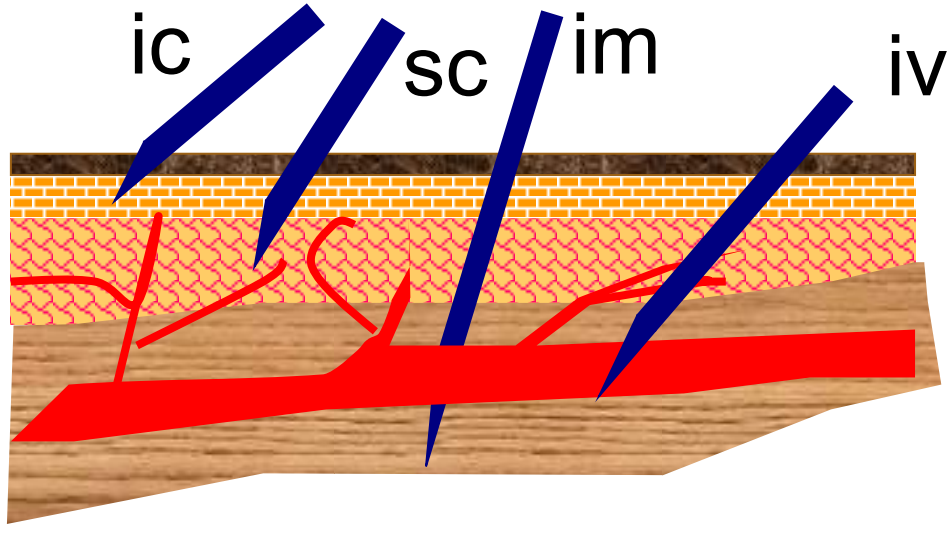
Delivered as injection

- Intravascular
  - Intra venus (IV common)
  - Intra arterial (difficult)
- Intracutaneous (ic) or intradermal
- Subcutaneous (sc)or hypodermic
- Intramuscular (im)



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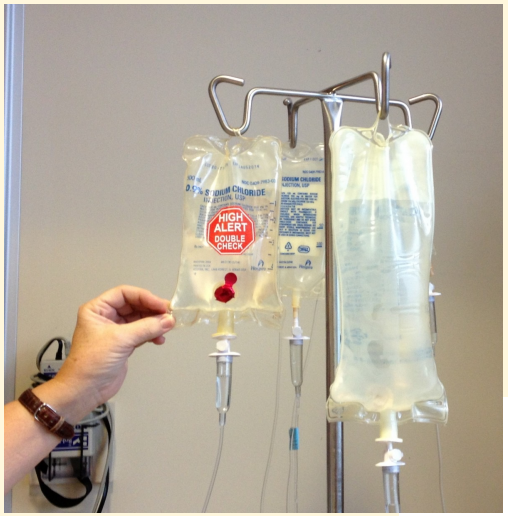
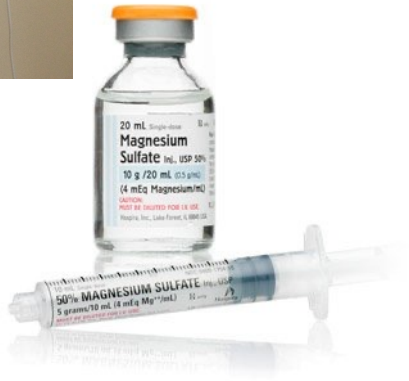
Intra venus





- Administered using an intravenous catheter or needle
- Given as bolus injections or continuous infusions.
- Rapid effects
- 100% of dose to systemic circulation
- High risk of infection or adverse reactions
- Volume of injection
  - Injection of max 20 ml
  - Infusion of min 250 ml

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Subcutaneous

- SC injections are often given using a short needle,
- The drug is absorbed slowly into the bloodstream through the capillaries in the subcutaneous tissue.
- Well-tolerated and less painful than some other injection routes.
- Allows for self-administration
- Lower risk of accidental intravascular injection
- Volume ≤1 ml

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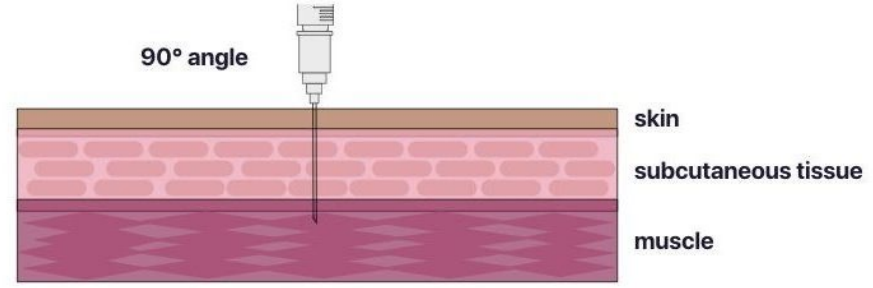
Intramuscular



- The drug is absorbed into the bloodstream from the muscle capillaries
- Faster uptake compared to sc administration
- Longer needles than SC.
- May cause more discomfort than subcutaneous injections
- Volume below 5 ml

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Risks related to injections

- Infection
- Adverse reactions
  - allergy
  - endotoxin
  - particles
  - ADA
- Bleeding and bruising
- Damage to nerves or blood vessels,
- The potential for accidental intravascular injection

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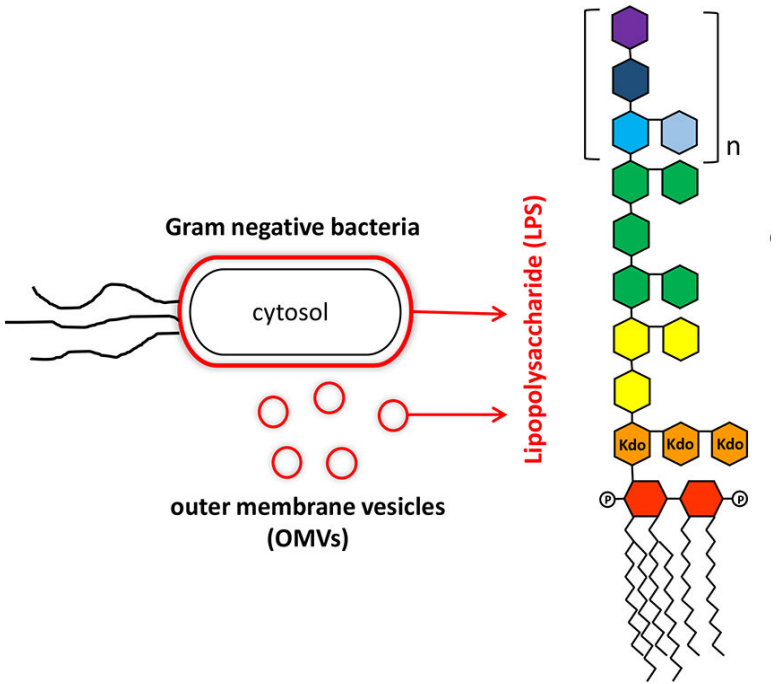
Pyrogens and endotoxins



- Substances that causes an inflammatory response
- Pyrogen - causing fever -Often endotoxin
- Endotoxin -lipopolysaccharides from dead gram-negative bacteria

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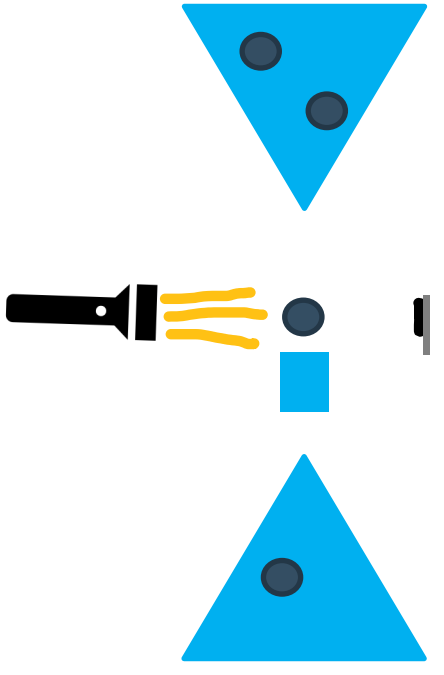
Safety -particles

Unknown particles can trigger

- Inflammation
- Immune response
- Clogging of small blood vessels
- Trapped in the alveolar blood vessels causing embolism

Tests for visual and sub-visual particles.

- Visual all containers
- Sub visual representative containers



Subvisual particles detected by light obscuration

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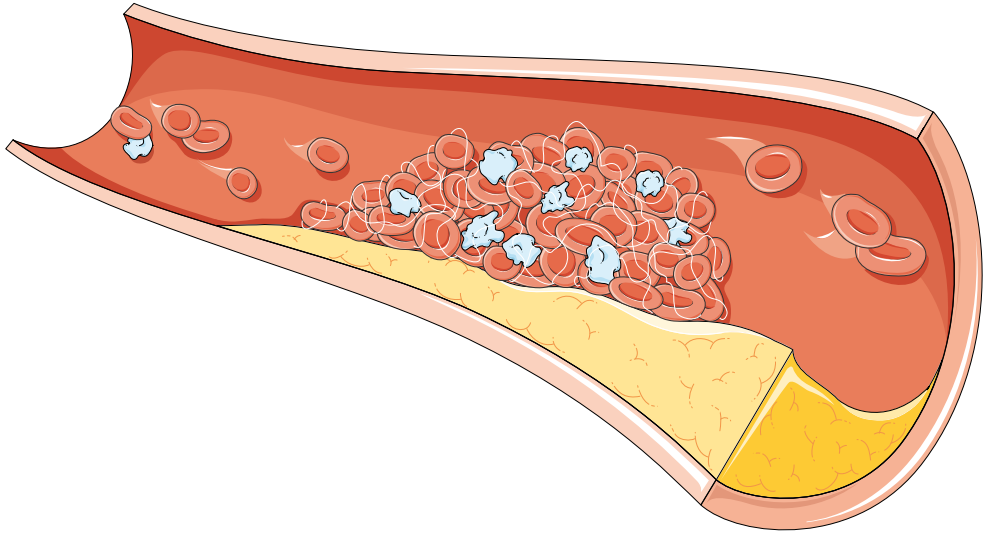
Blood clotting



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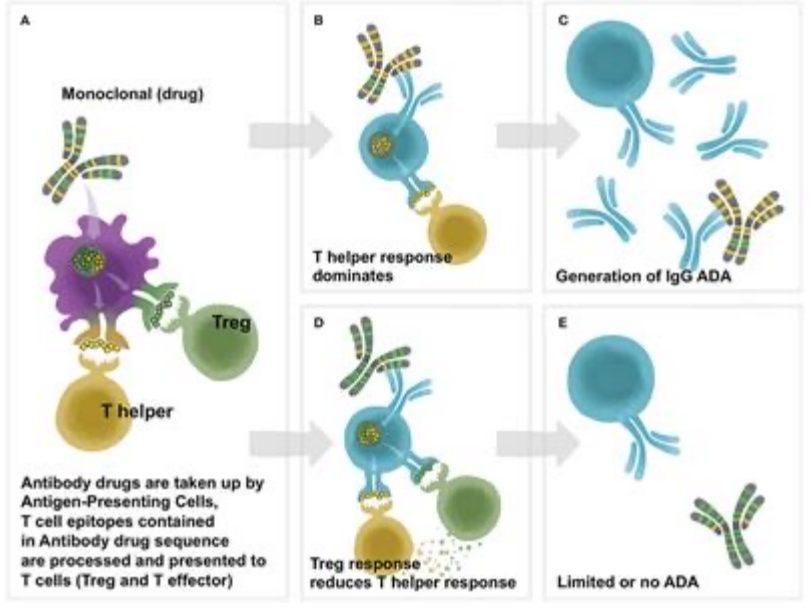
Anti-Drug Antibody (ADA)

Unwanted immune response of the host against the therapeutic protein

Two types of ADA

- non-neutralizing ADA
- neutralizing ADA



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Anti-Drug Antibody (ADA)

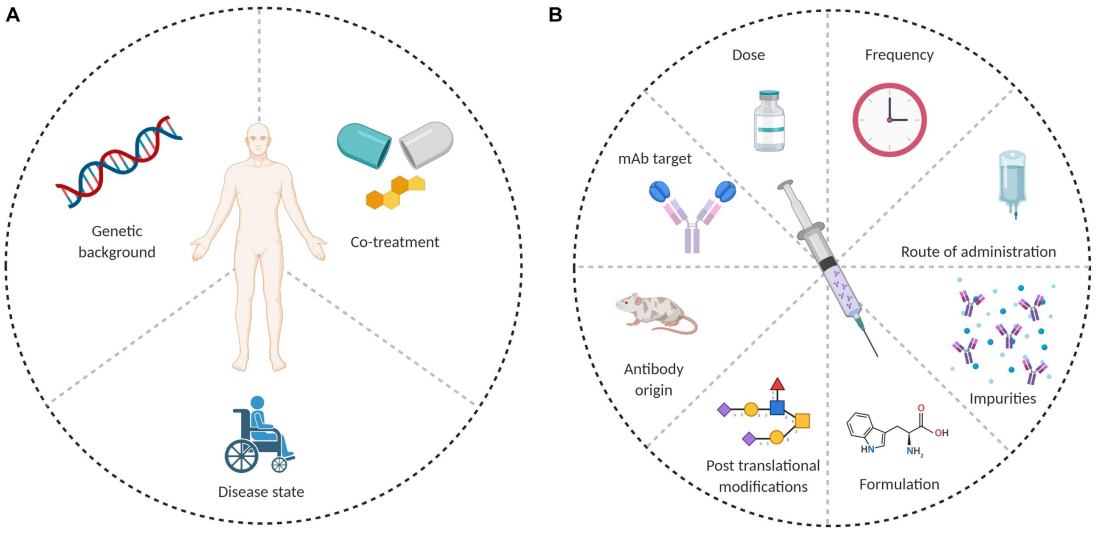
Unwanted immune response of the host against the therapeutic protein

Two types of ADA

- non-neutralizing ADA
- neutralizing ADA

Can lead to;

- Loss of activity
- Changes in pharmacokinetics- faster clearance
- Immunological reactions to infusion
- Immunity against endogenous proteins



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Real World Handling of Protein Drugs – Exploration, Evaluation & Education

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