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Challenges of IV in-use stability for Biologics
Some case studies

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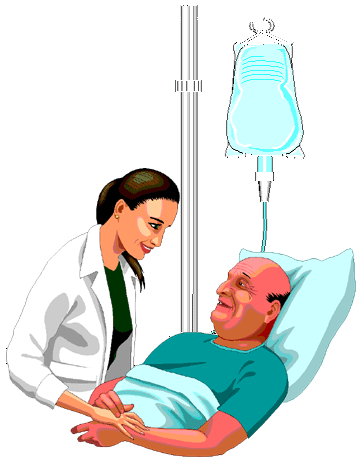
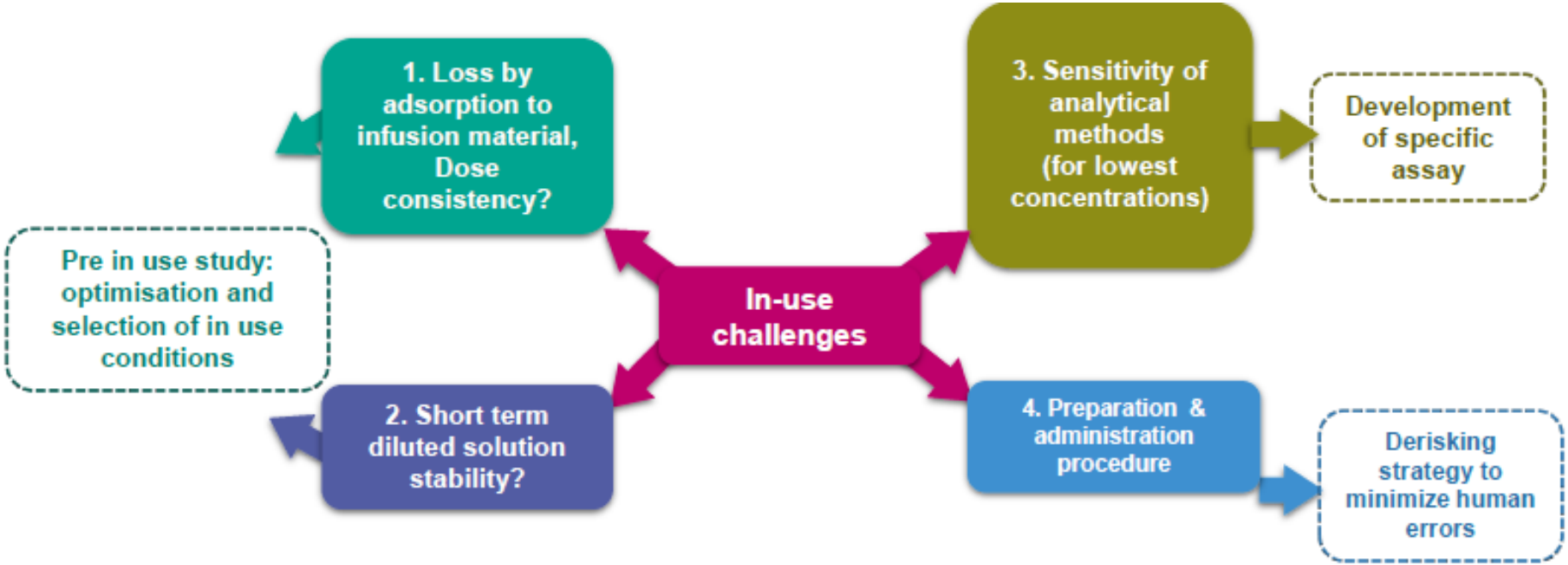
IV In-use studies

- **The objective of these studies is to provide information to users about the preparation, storage conditions and utilization period of drug products**
  - Concentrate or powder (lyophilisate) for solution for infusion
  - Parenteral administration by intravenous injection
- **They are based on clinical study design and interactions with clinicians**
  - In accordance with the target product profile
  - For elaborating of the pharmacy manual
- **Usual questions are:**
  - How long can I store the drug outside of the fridge?
  - How should I reconstitute the lyophilisate?
  - How stable is it after reconstitution?
  - In which infusion bag can I dilute the product?
  - How long is it stable after dilution?
  - Can I use my usual infusion pump and infusion set?
  - Which in line filter should I use?



IV In-use challenges



Properly designed IV in-use studies

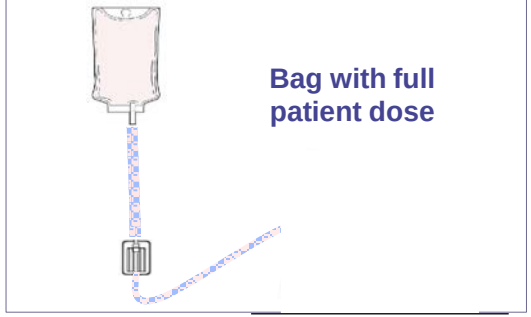
- **Pre-in use studies**
  - De-risk “formal in-use” studies to identify potential stability challenges
  - Anticipate pharmacy manual requirements
    - Impact of DP dilution
      - Critical to understand lowest doses: higher risk of adsorption, dose accuracy, …
    - Compatibility with infusion material
    - Diluent type (NaCl or Dextrose)
    - Effect of holding time and temperature

- **Formal in-use studies**
  - Results are described in a dedicated paragraph of the pharmaceutical development section in submission dossiers (IND, IMPD, or BLA)
  - Support Pharmacy manual preparation

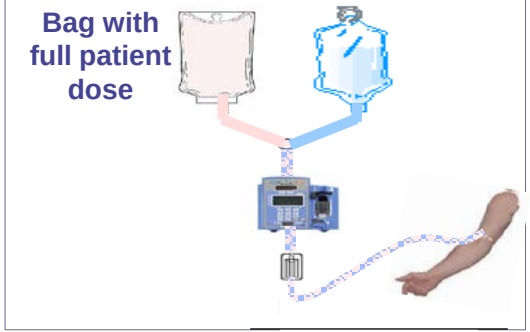
Properly designed IV in-use studies

- **Different administration modes**

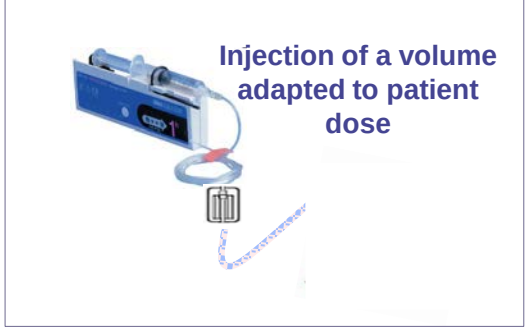
Gravity



Infusion pump



Syringe driver



Properly designed IV in-use studies

- **Main parameters needed to design IV in-use studies**
  - Minimum and maximum dose
    (derived from dose escalations and patient weights)
  - Minimum and maximum infusion rate
  - Minimum and maximum infusion duration
  - Diluents (NaCl 0,9% or Dextrose 5%)
  - Holding times and temperatures before application
  - Diluted product concentration ranges
  - Administration volumes
  - Material for infusion system, tubing, filter

Mainly clinical inputs

Mainly formulator inputs

Cooperative effort between a clinical team and a formulation team to define the parameters.
Good design and preparation for an in-use study will ensure proper execution to achieve its goals, change of one parameter can imply to re-do all in-use studies.

Properly designed IV in-use studies

- **Quality attributes followed**
  - Coloration, pH
  - Protein concentration
    - A280 or IgG ELISA for very diluted products
  - Purity
    - SEC; SEC can be difficult for very diluted products
  - Visible particulate matter
    - Visual inspection
  - Subvisible particulate matter
    - Light obscuration
  - Relative potency
    - Binding or cell-based assay; binding can be difficult for very diluted products
  - For ADC : Drug to Antibody Ratio (DAR), free drug content
  - Microbiology
    - If storage duration >4h at RT or refrigerated

Properly designed IV in-use studies

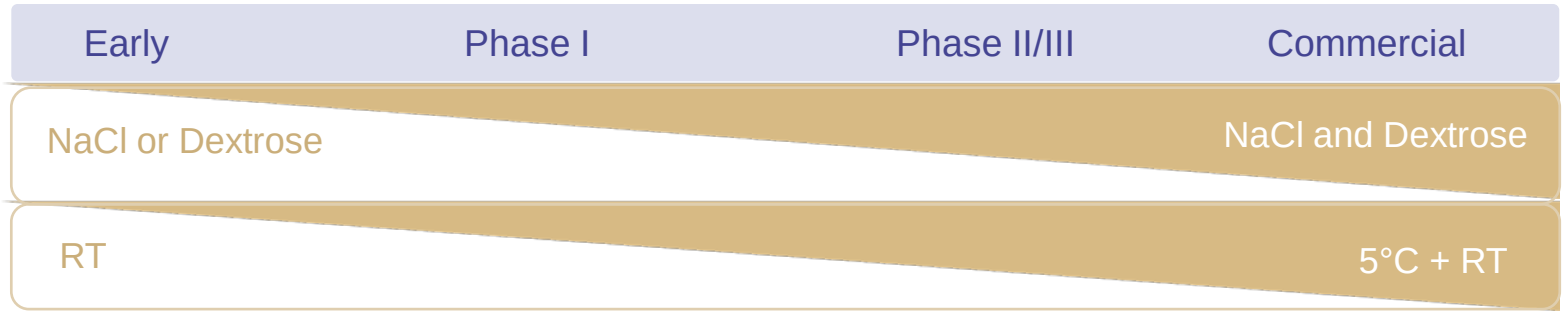
- **Infusion material**
  - Stability is defined by type of component for bag, infusion set and filter

	Polymer materials
Infusion bag	PO + PE + PVC with DEHP + PP + EVA
Tubing line	PE + PVC/DEHP + PVC DEHP free (with TOTM or DEHT) + PUR + PBD
In line-filter	PES + PS + nylon

PVC: polyvinylchloride
PP: polypropylene
PE: polyethylene
PO: polyolefin (PP+PE)
PUR: Polyurethane
DEHP: Di(2-ethylhexyl) phtalate
TOTM: Tris (2-Ethylhexyl) Trimellitate
DEHT: Dioctyl terephthalate
PBD: polybutadiene
PES: Polyethersulfone
PS: Polysulfone

Properly designed IV in-use studies

- **Diluents selection**
  - NaCl 0,9%: effect of dilution
  - Dextrose 5%: effect of dilution, glycation
- **Holding time impact**
  - Refrigerated
  - RT (Room Temperature)

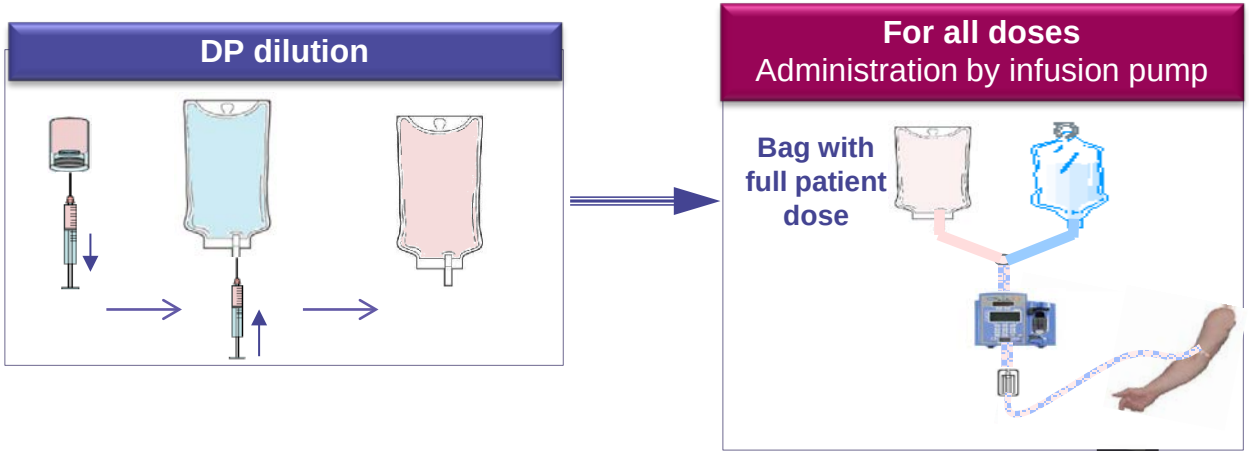


Points to consider for pre in-use studies

- Pre in-use studies are an essential component of formulation selection
- Surfactant from DP can potentially be diluted below CMC
  - Use pre-in use data to adjust DP composition
  - Add surfactant coating solution (a second DP to be developed)
- Analytical methods may be adapted to the concentration levels in the infusion bags
  - Specific quantification methods could be needed (e.g. ELISA)
  - Coating with surfactant solution may be needed for low concentration analytical samples

Case study 1 – Administration of a mAb by infusion pump

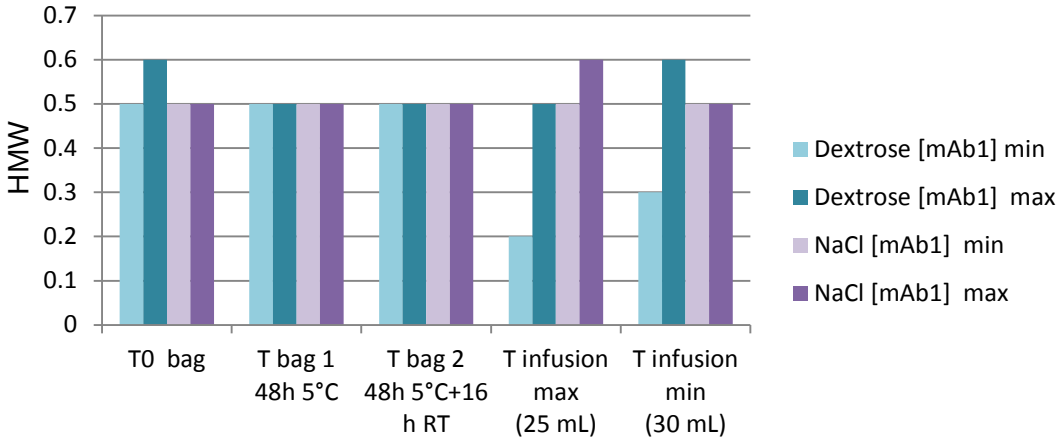
Preparation and administration procedure

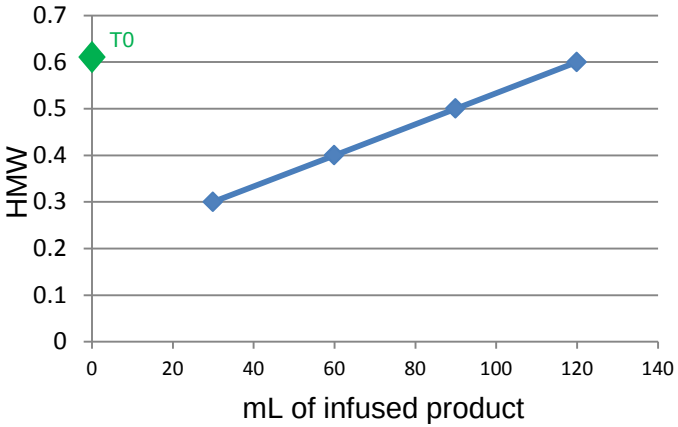


In-use studies in NaCl and Dextrose at min and max concentration of diluted product were performed.

Case study 1

%HMW results





Soluble aggregates (HMWs %) are constant in all conditions except after infusion at min mAb1 concentration in Dextrose 5%, where lower levels of HMWs were observed after infusion.

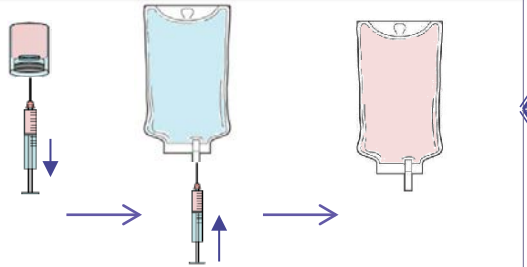
Values of HMW% decreases in the first mL due to adsorption (infusion set or filter). Values of HMW% retrieve their initial value when around 120 mL are infused.

Less HMW is not critical, no mitigation is put in place

Case study 2 – Administration of an antibody-drug conjugate

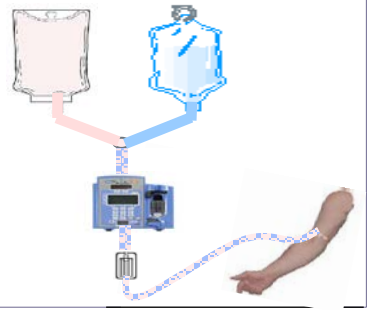
Preparation and administration procedure

DP dilution



For high doses
Administration by infusion pump

Bag with full patient dose



For low doses
Administration by syringe driver

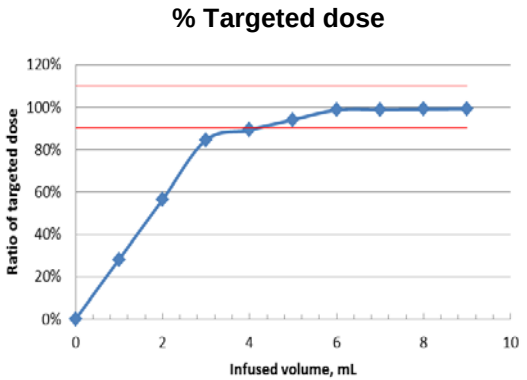
Injection of a volume adapted to patient dose

Low doses cannot be injected from pre-filled bag of diluent
→ Very low product concentration, below analytical thresholds for control

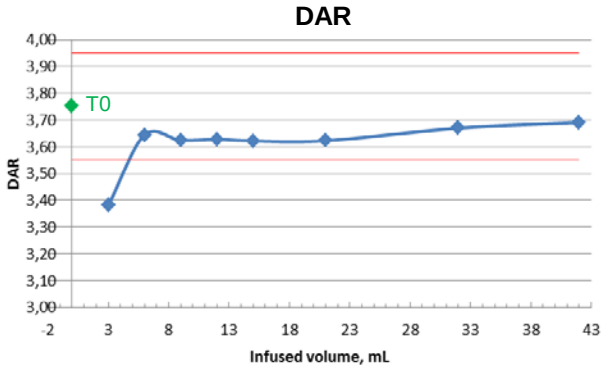
Challenge for low doses : accuracy of dosing
- Impact of dead volume in the tubing
- Level of adsorption onto tubing and filter

Case study 2

ADC dose and drug/antibody ratio (DAR) as a function of infused volume



The required dose (at +/-10%), is ensured only for volumes >4mL. Below 4 mL, flush is necessary



The required DAR at 3,8 +/-0,2, is ensured only for volumes > 6 mL

For low doses, a flush of 25mL of the diluted active (safety margin to cover different infusion set dead volumes) is required to overcome adsorption issues in order to ensure the delivery of the targeted dose

Ph1 clinical studies de-risking strategy built on 3 axis to minimize human errors

1. Careful selection of sites for study initiation and limitation of the number of sites for escalation phase

2. Definition/optimization of administration protocol to minimize human errors by integrating feedback from clinics (incl. clinical supplies and clinical site):
    - Use same dilution approach for all doses as much as possible
    - Keep it simple

3. Providing clear instructions and training on-site:
    - Review of preparation and clinical administration documentation included in the Pharmacy manual
    - Preparation of a short video if needed
    - On-site training before 1st patient treated

Take Home Messages

- **Drug product development**
  - In-use studies are an essential component of formulation selection and to design preparation and administration procedures
  - In addition to platform formulation the use of platform components contribute to simplify in-use study
- **In-use studies**
  - Precise expectations from clinicians and pharmacists
  - Keep it simple (HA may consider complex dilutions as a GMP manufacturing step)
  - Not all products and impurities behave the same
- **Analytics**
  - Usual analytical methods may not be suitable for assessing stability of low concentration solutions

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