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

DDF Berlin March 11-13th 2019 - H. Audat
Properly designed IV in-use studies

• **Definition of in-use studies**
  - The purpose of in-use stability testing is to provide information to users about the preparation, storage conditions and utilization period of drug products (e.g. reconstitution or dilution of a solution).

• **Biologics IV in-use studies**
  - For injectable: Drug Product (DP) is a concentrate for solution for infusion.
  - Aim: provide stability data for diluted DP after dilution in infusion bags and during administration through infusion set.
  - Evaluate compatibility with each recommended diluent and administration system, at the extremes of the recommended dilution ratios for the permitted duration of storage.
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• Different administration modes

- **Gravity**
  - Bag with full patient dose

- **Infusion pump**
  - Bag with full patient dose

- **Syringe driver**
  - Injection of a volume adapted to patient dose
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, tubings, filters

Cooperative effort between a clinic 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.
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• **Pre-in use studies**
  • De-risk “formal in-use” studies to identify potential stability challenges
  • 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**
  • In GMP environment
  • Results are described in a dedicated paragraph of the formulation development section in submission dossiers (IND, IMPD, or P2.2 section of BLA)
  • Support Pharmacy manual preparation
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• **Quality attributes followed**
  - Coloration, pH
  - Protein concentration
    - A280 or SoloVPE 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 and if > 24h refrigerated

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

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

**Polymer materials**:
- 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

**Early**
- Few platform components

**Phase I**

**Phase II/III**
- Extended material components

**Commercial**
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)

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<th>Phase I</th>
<th>Phase II/III</th>
<th>Commercial</th>
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<tr>
<td>NaCl or Glucose</td>
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<td></td>
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<tr>
<td>RT</td>
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<td>5°C + RT</td>
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Case 1 study

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<th>Adsorption cases</th>
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<tr>
<td>ADC2</td>
</tr>
<tr>
<td>mAb3</td>
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</table>
mAb1 - HMW adsorption

Preparation and administration procedure

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

For all doses
Administration by infusion pump

Bag with full patient dose
mAb1 - HMW adsorption

%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
### Adsorption cases

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<td>HMW adsorption in Dextrose at low concentration</td>
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<td>ADC2</td>
<td>Preferential adsorption of ADC with high DAR</td>
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<tr>
<td>mAb3</td>
<td>Protein adsorption for a highly diluted preparation</td>
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</table>
ADC2 – Preferential adsorption of ADC with high DAR

Preparation and administration procedure

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
ADC2 – Preferential adsorption of ADC with high DAR

ADC concentration and DAR in syringe driver (worst-case)

To retrieve the initial concentration of the infused product, 6 mL of diluted product is necessary.

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 > 9 mL. Adsorption of high DAR species (due to higher hydrophobicity)

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 and product.
## Adsorption cases

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mAb3: highly diluted preparation

Preparation and administration procedure

For low doses
Administration by syringe driver

For high doses
Administration by infusion pump

Coating of infusion bag

1st bag
Solution for coating

1st DP dilution
1st coated bag
\( \mu g/mL \)

2nd bag
Solution for coating

2nd dilution
2nd coated bag
\( \mu g/mL \)

Bag with full patient dose

Injection of a volume adapted to patient dose

Solution for coating

1st bag

Solution for coating

2nd bag

mAb3: highly diluted preparation

Evaluation of adsorption in infusion bags

Bags w/wo surfactant:
- 0 ppm
- 100 ppm

Bag precoating with 100 ppm of surfactant prevents adsorption at ng/mL ranges

Bag precoating with surfactant allows to prevent adsorption issue
mAb3: highly diluted preparation

Selection of filter and [surfactant] for syringe driver

Less adsorption with filter 2 vs filter 1. Significant adsorption in the 1st samples for bags containing 20 and 50 but not with 100ppm of surfactant.

Surfactant concentration has a significant impact on adsorption to infusion material (filter, tubing). At least 100 ppm needed to efficiently prevent mAb adsorption. Filter 2 was selected for the syringe driver procedure.
Conclusions

• All factors to design the IV in-use studies are crucial and need to be validated between clinics and formulators.

• Pre in-use studies are necessary to derisk in-use studies and to design preparation and administration procedures.

• The behavior of different modalities (e.g. low doses, ADC, ...) and impurities need to be specifically evaluated in terms of adsorption to in-use materials.

• Perspective of in-use
  • Some additional DP handling stresses should be also evaluated/assessed linked to handling of DP container and prepared bags (e.g. closed system drug transfer devices, pneumatic tubes, ...).
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