CMC Aspects When Switching from Intravenous to Subcutaneous Formulations

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Disclosure and Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and do not necessarily reflect the view of the AGES and/or the EMA.

Overview of this Talk

- My background
  - Quality assessor for biological medicinal products (with focus on on therapeutic recombinant proteins) since 2009
  - Centralised Procedures & Life Cycle
  - National and European Scientific Advice procedures
- The following presentation will discuss (blinded) case studies addressing quality challenges in the development of intravenous (IV) to subcutaneous (SC) formulations from a regulatory point of view

Case Study 1

Process Qualification Strategy

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Background

- Monoclonal antibody approved in EEA and numerous other countries
  - as a powder for concentrate for solution for IV and
  - as a solution for injection for SC administration available as a pre-filled syringe and autoinjector pen
- Additional DS manufacturing capacity is needed to meet the growing demand for the IV and SC products
  - The MAH plans to introduce an additional site for manufacture of DS for both formulations (IV and SC)
  - DS manufacturing process is identical for the IV and SC formulations until the last step (final UF/DF, formulation and concentration)

Case Study 1

Process Qualification Strategy

The MAH proposes to qualify the new site by employing a "matrix PPQ approach" including three consecutive runs:

- One IV batch and two SC batches
- DS manufacturing process is identical for the IV and SC formulations until the final UF/DF, formulation and concentration step.

Case Study 1

Process Qualification Strategy

- Validation studies will be conducted
  - Once for the IV process and
  - Twice for the SC process (due to the higher degree of complexity compared to the IV process).
  - The two SC batches will run in one harvest/purification train each.
  - Process monitoring under the continued process verification protocol (post-approval) will be used to collect additional data from the initial commercial batches post-PPQ for the final formulation-steps.

Case Study 1

Process Qualification Strategy

Does the Agency agree to the process qualification strategy?

- Acknowledged that the largest part of the IV and SC process are identical and only differ with regard to the last process step.
- Proposal for the PPQ strategy using 1 IV lot and 2 SC lots could be acceptable.
- At time of submission sufficient justification should be provided why 2 SC lots and 1 IV lot is considered sufficient to conclude on the PPQ of the two process variants.
- It cannot be excluded that data from additional PPQ lots may be required, e.g. in case of deviating results between SC and IV data.

Case Study 2

Manufacturing Process

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Background

- Monoclonal antibody developed as a biosimilar medicine
  - Currently approved as IV presentation (powder for concentrate for solution for infusion)
  - MAH is developing a SC administration form (solution for injection)
  - Development of a novel formulation to circumvent the patent blocks on the innovator product formulation
  - Major differences between SC and IV formulations are:

Case Study 2

Manufacturing Process

1. Dosage form
2. Higher concentration of DS in the SC presentation (approx. 4 – fold higher)
3. Quantitative and qualitative composition

Manufacture of drug product

- No change is planned related to the DS (the same DS will be used IV and SC presentation)
- Concentration of DS will be increased by tangential flow filtration (TFF) during the drug product manufacturing process
- TFF step will be preceded by a cation exchange chromatography (CEX) step aimed at removing excipients from the DS that will not be part of the SC formulation

Case Study 2

Manufacturing Process

Is the proposed manufacturing process of SC drug product considering the differences between SC and IV drug product acceptable?

- Efficiency of TFF and CEX steps (included to remove excipients from the DS that will not be part of the SC formulation) to consistently generate a DP with the expected composition will have to be demonstrated.
- Appropriate process validation studies must be conducted (including demonstration of clearance of unintended excipients from the DS).
- Suitable in-process controls must be implemented.
- Apart from adequate process validation studies, an appropriate DP comparability study - IV versus SC presentation - should also be conducted.

Case Study 3

CMC Comparability

- Monoclonal antibody under development focused on the treatment of patients with auto/alloimmune and inflammatory diseases
- The Applicant is planning to change from the Process 2 DS/DP final vialed product for IV administration being used in ongoing Phase 2 clinical studies to Process 3 DS/DP final vialed product for SC administration and DP pre-filled syringe (PFS) for SC administration for use in future Phase 3 clinical studies

Case Study 3

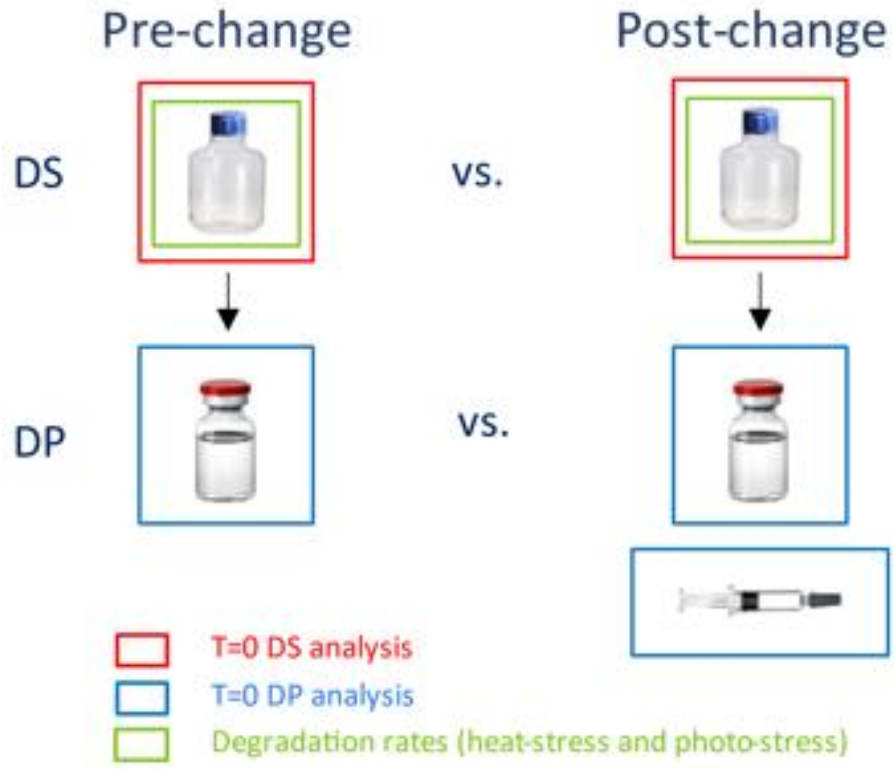
CMC Comparability

- The applicant intends to implement a DS manufacturing process with a higher yield that would allow a DP manufacturing process for IV and SC administration
- Major changes are introduced in the DS manufacturing process (e.g. new high titer producing cell line, new media, different formulation, higher concentration) which also impacts the DP manufacturing as well as DP quality as the DS concentration is increased.

Case Study 3

CMC Comparability

- To support the Process 2 (ongoing Phase 2) to Process 3 (planned Phase 3) process changes a comparability study will be performed



Case Study 3

CMC Comparability

- One pre-change DS and one post-change batch of DS and
- One batch of pre-change DP (vial) and one batch of each DP presentation (vial and PFS) will be evaluated
  - Batch release results will be compared to the release acceptance criteria
  - Characterisation results will be evaluated based on method performance and product knowledge
  - The release and characterisation results will also be compared to available historical data using actual ranges (minimum-maximum) and statistical ranges where possible.
  - A head-to-head degradation rates study using 1 pre-change and 1 post-change batch of DS will be used to evaluate stability under heat-stress (5 °C, 25 °C, and 40 °C) and photo-stress storage conditions.

Case Study 3

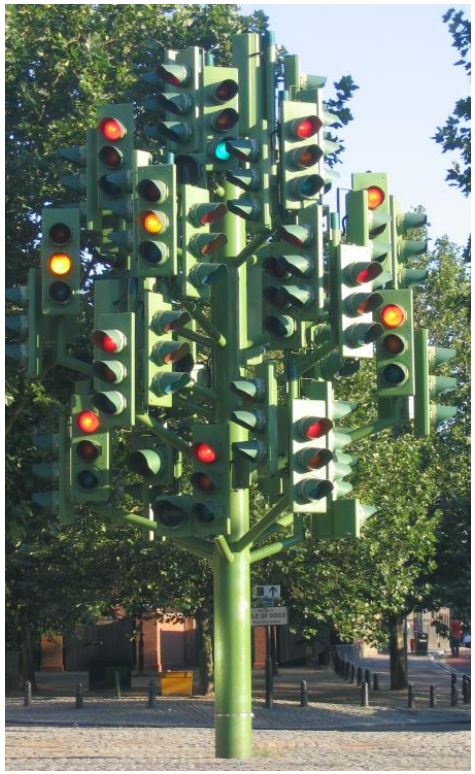
CMC Comparability

Is the comparability approach - Process 2 DS/DP for IV versus Phase 3 DS/DP for SC administration - acceptable?

- Proposed number of batches to be included in the comparability exercise is not considered sufficient.
- For comparison of Process 2 final vialed product to Process 3 final vialed product it is recommended to include more batches into comparison.
- Regarding the additional DP pre-filled syringe it might be acceptable to include just one batch considering that the DS manufacturing process and the composition is the same.

Thank You for Your Attention

The floor is yours



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