Considerations for Control Strategies for mAb/mAb Combination Therapies – An Industry Perspective

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• Acknowledgements
• Benefits to Patients of Combination Therapies
• Combination Therapies – *Differences Matter*:
  • Nomenclature
  • Combinations
  • Administration
• Examples:
  • Analytical Methods
  • Acceptance Criteria – Cumulative Impact Assessment
• Conclusions
Acknowledgments

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Benefits for Patients

• Many diseases are treated with combination therapies:
  • multifactorial causes
  • interlinked or parallel molecular pathways
  • improved efficacy or safety profiles
  • dosing/ patient convenience

• However, combination therapies are often evaluated after approval of individual medications

• There is a need for their early evaluation (i.e. prior to approval) for complex and life-threatening diseases
• **COMBINATION PRODUCT** - Two or more regulated components, that are physically, chemically combined as a single entity or packaged together in a single package (example: drug / device)

• No clear Health Authority definitions on what constitutes a “Combination Therapy” and what differentiates them

• There is currently no CMC guideline specific for combination therapy, except WHO’s for small molecules

• Roche/Genentech Internal Usages:

  • **COMBINATION THERAPY** - Two or more medicines administered as part of a therapy to treat a specific condition:
    
    • Separate Administration
    
    • Simultaneous Administration
Many permutations with different complexities are possible.

Suitable nomenclature is needed to effectively manage this complexity.

Roche/Genentech Internal Nomenclature:

<table>
<thead>
<tr>
<th>Simultaneous $\leq 60$ min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fixed dose</strong></td>
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</tbody>
</table>

- **fixed dose**
  - single pharmaceutical form
  - 
  - A + B

- **co-mixture**
  - co-mixed at the clinical site
  - individual/ co-packed
  - mixing: IV bag, vial, syringe
  - A + B

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- break-time between individual injections of A then B $\geq 60$ min
  - A + B
## Dependencies of CMC Complexity

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<td>commercial</td>
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### Increased CMC Complexity

- A
  - clinical
  - commercial
- B
  - clinical
  - commercial
Combination Therapies & Analytical Methods
• DS release and stability methods are typically *not* impacted:
  • DS are manufactured and stored separately
  • but, DS manufacture for fixed-dose DP must be understood

• **DP methods can be partially/ fully impacted:**
  • fixed dose → release and stability
  • co-mixture → in-use stability, e.g. IV bag
  • Separate/ individual DP administration has no method impact
API Methods – Combination Therapies (II)

- **Possible Impact to Single Product Methods:**
  - Partial/complete analytical interference:
    - qualitative and quantitative sample read-outs:
      - chromatographic, electrophoretic, potency,…
    - *New* isoform formation due to protein A/ protein B interactions:
      - interference with mAb profiles and vice versa

- **Risk-based:**
  - The more similar the molecular make up of the products
  - The less discriminatory the analytical technique used
Analytical Methods – Charge/ 2 Mabs combined

- Does the partial separation suffice for DP release and stability testing?
- How to set suitable acceptance criteria, e.g. acidic region?
API Methods – Size/ 2 mAbs Combined

- Could absence of separation of A, B constitute a suitable method?
- How to set suitable release and stability criteria?
- Could the sum, e.g. of aggregates A + B be specified?
Combination Therapies & Cumulative Impact Assessment
The performance of a combination therapy could be undesirably impacted due to the combination of their constituents A, B,…:

- cumulative effects
- synergistic effects
- product-related impurities
- process-related impurities
- contaminants

Risk-based impact assessment should be performed:

- theoretical and/or experimental

Risk dependents on:

- administration type for combination therapy
- characteristics of constituents
- indication
- patient population
• Separate administration of two biologics, with one or more marketed products, including ≥60 min wait time:
  • no special considerations due to established safety profile of marketed product
  • only applicable for similar indications and patient populations
  • decreased risk to patients as a result of the 1 hour break time

• Administration of two biologics, within <60 min wait time:
  • Physicochemical attributes and impurity levels should not exceed those expected for a single product
• **Compendial pyrogenic dose limit:**
  • \( \leq 5 \text{ EU/kg body weight/ hour, for parenterals} \)
  • others, e.g. for intrathecal

• **Separate \( \geq 60 \text{ minutes} \):**
  • there is no further impact assessment required
  • single agent acceptance criterion are not impacted

• **Simultaneous \( \leq 60 \text{ minutes} \):**
  • individual endotoxin AC must be assessed to meet, when combined, pyrogenic dose limit

• **Fixed-dose:**
  • direct testing at final DP level
  • might require additional assessment of DS limits or DS lot selection

• **Co-mixture:**
  • assessed at individual agent DP level
  • might require lot selection, if sum of acceptance criteria exceed dose limit
• **Possible Risks Associated with HCP:**
  - immunogenicity/ safety
  - adjuvant – enhances immune response of DP
  - enzymatic activity – impact on product stability and efficacy

• **Challenges:**
  - there is no official generic limit, e.g. WHO
  - inherent complexity of HCP mixtures
  - analytical dependencies
  - time-break might not alleviate risks

• **Possible Strategies to Reduce Risk:**
  - DS lot selection – keep total DP HCP levels at a minimum
  - in-house generic phase-dependent HCP limits – keep sum within
  - commercial + clinical product + time-break – summation might not be needed
  - HCPs from different host cells – possibly less risk
Risk-based Approach – *In-use Stability Study, 24 h*

- 2 mAbs combined in saline IV bag
- partial overlap of charge profiles across all charge-based techniques
- No separation of mAbs using size-based techniques
- Assays known to be stability indicating

→ No change ≤ 24 hrs for both mAbs studied individually and co-mixed
Risk-based Approach – *High Molecular Weight Species*

- **Soluble aggregated forms of therapeutic proteins:**
  - can enhance immune response
  - lead to formation of anti-therapeutic antibodies
  - restrict sum of aggregates to tightest acceptance criterion of constituents

- **Simultaneous administrations require *special* consideration:**
  - possible formation of *heterologous HMWS*, defined as aggregates of product 1 and product 2:
    - potential increased immunogenicity
    - two target antigens being bound to an aggregated HMWS of two molecules.

- **Assessments can be performed as a theoretical exercise:**
  - knowledge of pathways involved in the MoAs
  - propensity of heterologous HMWS formation due to molecular make-ups, e.g. pI, hydrophobicity difference
  - experimental verification needed → extend depends on outcome of theoretical exercise
Summary

- There is a need for early evaluation of combination therapies for complex and life-threatening diseases

- The effective management and execution of CMC activities for combination therapies requires suitable and aligned nomenclature

- Combination therapies are created un-equal and warrant a risk-based and phase-dependent approach for their control systems with unique challenges

- Simultaneous vs separate administrations have different risk profiles

- Methods, shown to be suitable for an individual mAb, should be assessed for combination products – *What is a suitable separation?*

- Combination therapies require evaluation of acceptance criteria for individual single therapy products for contaminants, product- and process-related impurities – *What is a suitable acceptance criteria, e.g. A+B, A, B,…?*

- Molecular interactions between mAbs can occur and should be watched out for
Doing now what patients need next