The Role of Product-Specific Monographs in Biosimilar Product Development

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Analytical Considerations in Biosimilar Development

- Biosimilar manufacturers, regulatory authorities, and pharmacopeia organizations all share the common mission of delivering safe, efficacious, and affordable drugs to the patients.

- In comparison with originator biologic drugs, development of biosimilars needs to consider additional analytical requirements:
  - Regulatory: Demonstration of Analytical Similarity
  - Compendia: Compliance with Product-Specific Monograph

- To facilitate biosimilar development, it is important that regulatory authorities and pharmacopeia organizations align on regulatory and compendial requirements.
Regulatory Guidance on Biosimilarity

- General global alignment on regulation of biosimilars
  - Comparative assessment to a single approved/licensed Reference Product
  - Not identical, but highly similar notwithstanding minor differences that are not clinically meaningful

- Step-wise approach
- Totality-of-the-evidence

### Diagram

- Analytical
- Non-clinical
- Clinical PK/PD, immunogenicity
- Additional clinical study

unlock the
POSIBILITIES
unleash the
PASSION
Compendia Requirement – Product-Specific Monographs

- Product specific monographs is a “molecular dictionary”
  - Name
  - Definition
  - Identification
  - Tests and Acceptance Criteria
  - Compendia Reference Standard
  - Reference to General Chapters

= Quality Standards for Identity, Strength, Quality and Purity

**elephant**

noun ˈe-lə-phant
: a very large gray animal that has a long, flexible nose and two long tusks

Articles of different manufactures under the same definition/identification are governed by the same quality standards, but may differ in attributes not covered in the monograph.
Product-Specific Monographs – Generic Medicines

- Generic medicines
  - Identical in the active substance
  - Structure explicitly defined

- Role of product-specific monographs for small molecule generic medicines
  - Compendia specifications (tests and acceptance criteria) are typically sufficient to ensure product quality
  - Highly recognized Quality Standards that facilitate the development and approval of generic medicines
Product-Specific Monographs – Biosimilars

- Biosimilars
  - Identical primary structure for the principal species
  - Complex mixtures that are greatly influenced by the manufacturing processes

N-terminal heterogeneity
- Chemical modifications
- Fragmentation
- Disulfide related variants
- Glycosylation heterogeneity

Sequence variants

C-terminal heterogeneity
- Higher order structure
Product-Specific Monographs – Biosimilars

- Role of product-specific monographs for biosimilars may differ from that for generic medicines due to the complexity of biologic molecules
  - In early stage development, product-specific monographs facilitate biosimilar development by offering publicly available testing procedures, general quality profiles, as well as reference materials
  - Monograph requirements may overlap with, but do not provide assurance of, regulatory requirements for analytical similarity
  - In late stage development, product-specific monographs may be inadequate and even challenging to follow due to advancements in product understanding, process knowledge, and analytical methodology
    - Needs of improved control strategy
    - Regulatory requirements for demonstration of analytical similarity
How to Define Quality Standards for Biosimilars?

- Biologics are complex mixtures
  - 285 million possible isoforms for a mAb molecule \( (Steven\ Kozlowski,\ FDA,\ 2014\ Biotechnology\ Technology\ Summit) \)

Which mixture(s) should be used to define the quality standards of the molecule?
Which Attributes to Test?

- Critical Quality Attributes (CQAs) are those “physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality” - *ICH Q8(R2)*

- CQAs are the basis of:
  - Product control strategy
  - Biosimilarity assessment as they are “clinically meaningful”

- The CQA assessment and the corresponding control strategy by the biosimilar manufacturers are based on both public and *private* product and process knowledge

How to address continuous advancement in understanding of the molecule and its biology in product-specific monographs?
What Test Procedures to Use?

- Regulatory guidelines emphasize on the use of best available analytical methods to demonstrate biosimilarity
  - EMA: “establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar.”
  - FDA: “A meaningful assessment as to whether the proposed product is highly similar to the reference product depends on, among other things, the capabilities of available state-of-the-art analytical assays…”

How to address continuous advancements in analytical technologies in product-specific monographs?
### Product-Specific Monograph - Tests

Analytical testing of the same molecule evolves over time driven by advancements in analytical technology, as well as the understanding of the product and its biology.

#### Hypothetical Example

<table>
<thead>
<tr>
<th>Monograph Methods</th>
<th>SDS-PAGE</th>
<th>RP-HPLC</th>
<th>IEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attribute</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative Methods</td>
<td>CE-SDS</td>
<td>RP-UPLC</td>
<td>CEX</td>
</tr>
</tbody>
</table>

- More quantitative
- Automation
- Speed
- Better separation between certain critical and non-critical degradant peaks
- More quantitative
- Addressing additional CQAs

“Alternative Methods” provide
- Better control strategy
- Better assessment of analytical similarity

However, the burden is on the manufacturer to demonstrate that the “new methods” are equivalent or noninferior to monograph methods for all attributes, which can be problematic in the example case of UPLC vs. HPLC above.
Differences between Monograph and Regulatory Requirements

- Monograph requirement: If identity met, then quality standards apply
  - if tested, and regardless if a compendia designation (e.g. USP) is claimed by label or not
  - through enforcement of regulatory authorities, but not the pharmacopeia organizations
Differences between Monograph and Regulatory Requirements

Monograph Requirement
- All individual impurity peaks must be NMT x%

Biosimilarity Requirement
- Similar with no clinically meaningful differences

Reference Product

Biosimilar A
- Potentially clinically meaningful

Biosimilar B
- Not clinically meaningful

CQA
Non-CQA
Differences between Regional Monograph Requirements

- Biosimilar products aiming at global market face the challenge of meeting different regional compendia requirements

Compendia Requirements

- There are no regional boundaries in scientific knowledge and technical advancement, which provides the foundation of harmonizing pharmacopeia quality standards. Aligned regional monograph requirements will relieve manufacturers’ burden of duplicating the efforts in meeting compliance requirements and divert more energy towards the goal of safe, efficacious, and affordable drugs to patients.
The Role of Compendia Reference Standard

- Compendia Reference Standard is a key component of the Monograph Quality Standard
  - Among other things, define potency units and acceptance criteria

- However, demonstration of analytical similarity requires comparison with the Reference Product
  - For example:
    - Compendia requirement: 80-125% relative to International Standard or USP RS
    - Regulatory requirement: Statistically equivalent to the results of Reference Product
Possible Role of Future Product-Specific Monographs

- In contrast to that for small molecule generic medicines, the role of product-specific monographs in biosimilar development should be adapted to accommodate the complexity of biologic drugs.

- CQA based monograph specifications
  - Allow alternative tests for a given CQA
  - Set acceptance criteria on level of CQA
  - For example:
    NOT: “Percent Peak X in Method A must be NMT 2.0%”
    BUT: “Percent oxidation of Met123 must be NMT 2.0%. Method A may be used to quantify Met123 oxidation”
Possible Role of Future Product-Specific Monographs

<table>
<thead>
<tr>
<th>Product Life Cycle</th>
<th>Requirement</th>
<th>Reference Product</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Filing</td>
<td>Regulatory</td>
<td>351(a)</td>
<td>351(k)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[Diagram showing additional clinical study, clinical PK/PD, immunogenicity, non-clinical, analytical]</td>
<td>[Diagram showing clinical PK/PD, immunogenicity, non-clinical, analytical]</td>
</tr>
<tr>
<td></td>
<td>Monograph</td>
<td>May not be available</td>
<td>Additional compliance requirement, if product-specific monograph is published</td>
</tr>
<tr>
<td>Future Process Change</td>
<td>Regulatory</td>
<td>Same comparability requirements would apply</td>
<td>Same monograph requirements would apply</td>
</tr>
<tr>
<td></td>
<td>Monograph</td>
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</table>

Monograph requirements enforced for biosimilar products would apply to originator’s reference product as well if process changes are to be introduced.
Conclusions

- For small molecule generic medicines, product-specific monographs have an established history of facilitating drug development and, together with regulatory requirements, ensuring drug safety and efficacy.

- For biosimilars, product-specific monographs need to adapt to the complexity of biologics in order to continue adding value to drug development and regulation:
  - Focus on drug definition and identification to avoid mislabels
  - CQA based specifications that offers flexibility to accommodate advancement in product understanding and analytical technologies
  - Use of compendial reference standards should be voluntary, especially for quantitative specifications including potency.
  - Alignments with regulatory requirements, as well as between regional pharmacopeia organizations.
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