Waiving in vivo studies for monoclonal antibody biosimilar development: National and global challenges

**Introduction**

- Biosimilars are biological medicinal products that contain a version of the active substance of an already authorised original biological medicinal product (the innovator or reference product).
- The first approved biosimilar medicines were small proteins, and more recently biosimilar versions of innovator monoclonal antibody (mAb) drugs have entered development as patents on these more complex proteins expire.
- There are currently major differences between how biosimilars are regulated in different parts of the world (Table 1), leading to substantial variability in the amount of in vivo nonclinical toxicity testing required to support clinical development and marketing of biosimilars.
- The European Union’s guidance describes an approach that enables biosimilars to enter clinical trials based on robust in vitro data alone; in contrast, guidance from the World Health Organization (WHO) is interpreted globally to mean in vivo toxicity studies are mandatory, though these guidelines are currently being updated.

**Table 1: Global regulatory environment**

<table>
<thead>
<tr>
<th>Global regulatory status in 2016</th>
<th>EMA</th>
<th>FDA</th>
<th>Health Canada</th>
<th>WHO</th>
<th>National guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated revision April 2015 (in vitro only), non-EEA (European Economic Area) reference product.</td>
<td>Updated revision April 2015, similar tiered approach to EU, suggest in vitro only acceptable.</td>
<td>New guideline finalised April 2015, similar tiered approach to EU, suggest in vitro only acceptable.</td>
<td>Recently suggested revisions recommend at least one repeat-dose in vivo study.</td>
<td>Interpreted as in vivo studies are mandatory.</td>
<td>Many based on WHO, interpreted as in vivo studies are mandatory.</td>
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</tbody>
</table>

**Working group aims**

- The NC3Rs and MHRA joint working group on mAb biosimilar development comprises 12 biosimilar manufacturers and CROs from Europe, USA, Canada, Korea, Japan, Russia and India, and 4 regulatory bodies (national and international). The group aims to:
  1. Share experiences and review current practices adopted during non-clinical development of biosimilar mAb products.
  2. Use the evidence-base to develop practical recommendations on when an in vivo study may or may not add scientific value for regulatory approval.
  3. Recommend a consistent approach to the use of animals during nonclinical assessment of biosimilar mAbs which can be used across all regions of the world.
  4. Disseminate the opportunities identified to minimise the number of non-human primates (NHPs) used in regulatory toxicology studies for biosimilar mAbs.

**Data collection and results**

- The group shared data on current practice and study design for 25 marketed and as yet unmarketed biosimilar mAbs that have been in development in the past 5 years, from a range of therapeutic areas (Figure 1).
- 8 products from 3 companies initially submitted in vitro only packages to regulatory bodies, though none of these were accepted.
- An in vivo toxicity study was carried out for all products, with varying study designs (Table 2).
- There were a total of 25 in vivo studies carried out for 25 products, with 2 in vivo studies in rats being conducted for one product.
- The majority (75%) of the in vivo studies were in NHPs, with the remaining studies carried out in rodents.
- Most common study design: 3M + 3F, 2 x high dose groups + control and 4 weeks (58%). Total = 18 NHPs (n range: 10 – 36) (Table 2).
- A minimised study design of 12 NHPs which did not include an untreated control group, was acceptable when in vitro alone has not been accepted.
- For all products, there were no differences detected between innovator and reference products in the in vivo studies.

**Conclusions and recommendations**

- There are practical challenges faced in obtaining regulatory approval for clinical trials based on in vitro data alone, despite some regulatory guidelines allowing this approach.
- The majority of reasons for carrying out nonclinical in vivo studies were not based on scientific rationale (Table 3).
- Where in vivo studies are required a minimum approach is recommended. For example, the relevant control for a biosimilar is the reference material, and therefore a vehicle control group is not necessarily needed, and the testing of a single reference product should be sufficient.
- Further work focuses on aim 4, to influence national practice and guidelines to enable opportunities for in vitro only approaches to be used and to accelerate global harmonisation in this area.

**Table 3: Reasoning given for in vivo studies: Not always scientifically driven?**

<table>
<thead>
<tr>
<th>Reasoning for in vivo studies</th>
<th>Scientific?</th>
</tr>
</thead>
<tbody>
<tr>
<td>In anticipation of a regulatory or institutional ethical committee request</td>
<td>×</td>
</tr>
<tr>
<td>Meetings with regulators not timely</td>
<td>×</td>
</tr>
<tr>
<td>Inconsistent approaches between geographic regions or within the same geographic region</td>
<td>×</td>
</tr>
<tr>
<td>Default practice to provide a comfort factor</td>
<td>×</td>
</tr>
<tr>
<td>Assessment of identified impurities</td>
<td>✓</td>
</tr>
<tr>
<td>To address a lack of in vitro data</td>
<td>✓</td>
</tr>
<tr>
<td>To address differences in the in vitro data between the reference and innovator</td>
<td>✓</td>
</tr>
<tr>
<td>Alternative formulations, novel excipients or higher concentrations of known excipients</td>
<td>✓</td>
</tr>
</tbody>
</table>

**3Rs impact**

- The working group have made recommendations for a data-driven approach to the toxicological assessment of mAb biosimilars that includes in vitro only approach where possible, or a minimised in vivo study design that minimises unnecessary use of animals and can be used across all regions of the world.

**Reference**