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

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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

Global regulatory status in 2016	
EMA	▪ Updated revision April 2015 (***in vitro* only**, non-EEA (European Economic Area) reference product). ▪ Specific guideline for mAb biosimilars, December 2012.
FDA	▪ New guideline finalised April 2015, similar tiered approach to EU, suggest *in vitro* only acceptable.
Health Canada	▪ Recently suggested revisions recommend at least one repeat-dose *in vivo* study.
WHO	▪ Interpreted as *in vivo* studies are mandatory. ▪ These guidelines are in the process of being updated.
National guidelines	▪ Many based on WHO, interpreted as *in vivo* studies are mandatory.

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 26 *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 (38%). Total = 18 NHPs (but 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.

Figure 1: Therapeutic areas

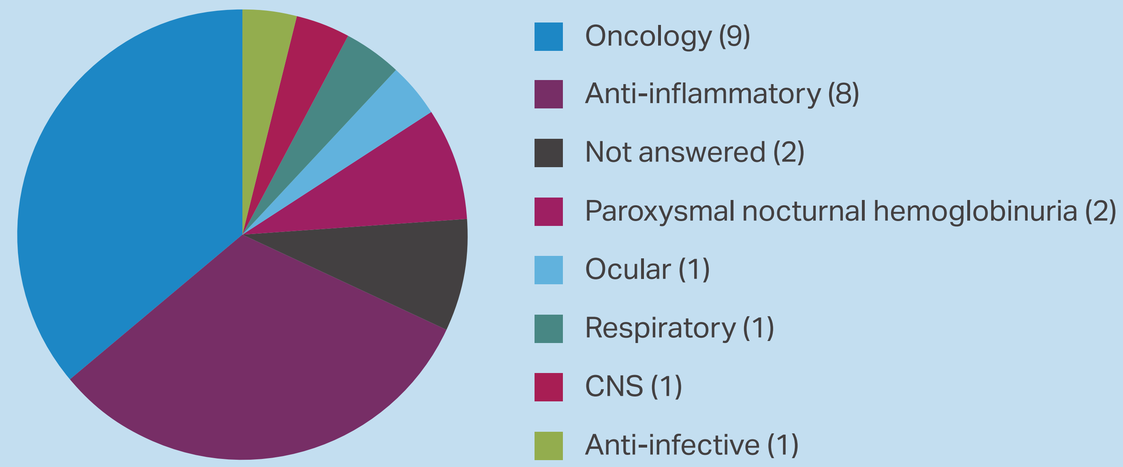

Table 2: Common study designs

Control	Biosimilar		Reference		Total # animals
	Low	High	Low	High	
		3M + 3F		3M + 3F	12
3M + 3F	-	3M + 3F	-	3M + 3F	18
3M + 3F	3M + 3F	3M + 3F	3M + 3F	3M + 3F	30

- Note, there were also examples of regulatory requests to test more than one reference material, which will increase the number of animal numbers used.

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?

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

3Rs impact

- The working group have made recommendations for a data-driven approach to the toxicological assessment of mAb biosimilars that includes an *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

Chapman K, Adjei A, Baldrick P, da Silva A, De Smet K, DiCicco R, Hong SS, Jones D, Leach MW, McBlane J, Ragan I, Reddy P, Stewart DI, Suitters A, Sims J. (2016). Waiving *in vivo* studies for monoclonal antibody biosimilar development: National and global challenge. *mAbs*. Volume 8, No. 3, 427–435.