# Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: **non-clinical** and clinical issues

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# Concept paper
# Non-clinical aspects to be addressed

**Step-wise approach** taking into account

- The outcome of the **quality** biosimilar exercise
- Specific **pharmaco-toxicological properties** of the reference product (RP)
- **Availability** of sensitive ***in vitro* assays** predictive for *In vivo* activity
- **Need and feasability** of additional ***in vivo* testing** taking into account 3 R principles

# Draft Guideline
# Non-clinical aspects

**Step-wise approach** for design of non-clinical study programme (as first introduced in the EMA biosimilar monoclonal antibody GL)

**Step 1**: ***In vitro* studies**

Comparative studies versus RP to cover the spectrum of expected pharmaco-toxicological effects

**Step 2**: **Determination of the need for *in vivo* studies**

Based on an assessment of all data available from the quality and NC *in vitro* biosimilar exercise

**Step 3**: ***In vivo* studies (only if indicated by step 2)**

Specifically designed to provide, if needed, complementary information taking into account 3R principles

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## Step 1: *In vitro* studies

***In vitro* assays** are often more specific and sensitive to detect differences between the claimed biosimilar and the RP than studies in animals and **are considered as paramount for the non-clinical biosimilar comparability exercise**.

**To detect any differences in biological activity between the claimed biosimilar and the RP,** the studies should

- be *comparative* in nature
- cover the *spectrum of effects* known to be relevant for the RP
- use a *concentration-range* where differences are sensitively detected
- be performed with an *appropriate number of product batches*
- use product *representative* of that intended for clinical use

**If the studies indicate relevant differences** versus the RP, **stand-alone development** should be considered

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## Step 2: Determination of the need for *in vivo* studies

**If the comparability exercise in the *in vitro* studies in step 1 is considered satisfactory and no factors of concern** (see below) **are identified in step 2, or these factors do not block direct entrance into humans, an *in vivo* animal study may not be considered necessary**

Some biotechnology-derived proteins may mediate *in vivo* effects that cannot be fully elucidated by *in vitro* studies

→ ***In vivo* studies** may be necessary in **selected cases** to provide complementary information

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## Step 2: Determination of the need for *in vivo* studies

**Factors to be considered** to assess the need for *in vivo* non-clinical studies include e.g.:

- **Presence of relevant quality attributes <u>not</u> detected in the RP**
  → e.g. new post-translational modification structures
- **Significant quantitative differences in quality attributes**
- **Relevant differences in formulation**

**If there is a need for additional *in vivo* information**

- the **availability** of a **relevant animal species** or **other relevant models** (e.g. transgenic animals, transplant models) should be considered
- if a relevant *in vivo* animal model is not available the applicant may choose to proceed to **human studies** taking into account principles to mitigate any potential risk

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## Step 3: *In vivo* studies (only if indicated by step 2)

The focus of the studies depends on the need for additional information.

Animal studies should be designed to maximise the information obtained. The **3R principles** should always be considered.

**PK and/or PD studies**
When the model allows, test and RP should be quantitatively compared (e.g. by concentration-response assessment)

**Safety studies**
A flexible approach should be considered, in particular if non-human primates are the only relevant species

→ e.g. in-life evaluation of safety parameters, just one dose level, just one gender, no recovery animals

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## Step 3: *In vivo* studies (only if indicated by step 2)

**Toxicity studies in non-relevant species** (i.e. to assess unspecific toxicity only, based on impurities) are not recommended

**Immunogenicity assessment** in animals
- is generally not predictive for immunogenicity in humans
- however, it may be needed for interpretation of *in vivo* animal studies

**Safety pharmacology, reproduction toxicity**, and **carcinogenicity studies** are not required for biosimilars

**Local tolerance studies** are usually not required unless excipients are used for which there is no or little experience with the intended clinical route