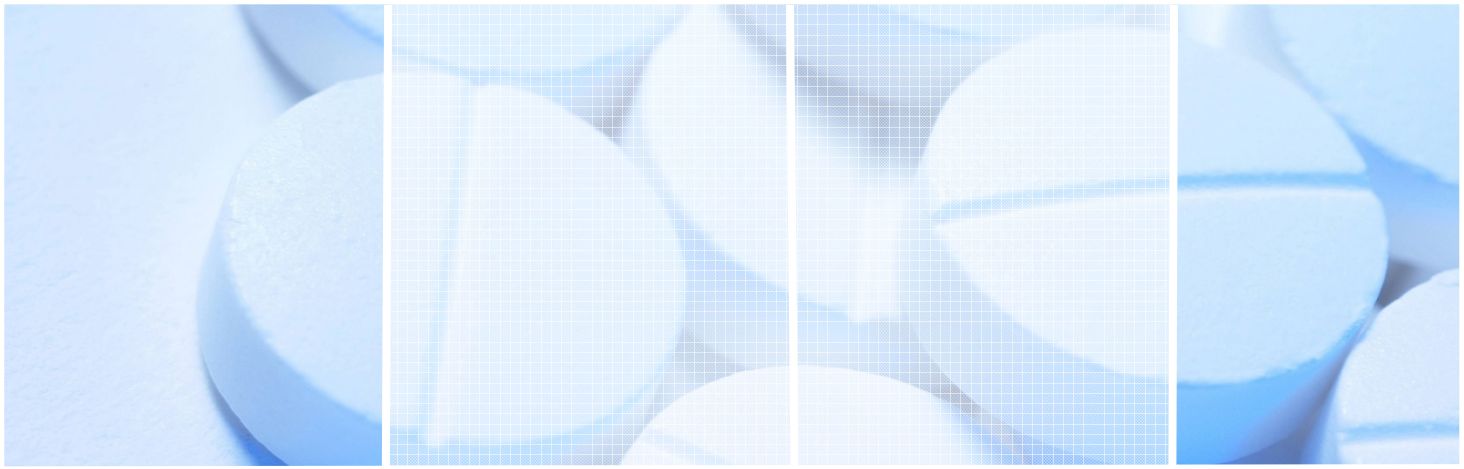

Federal **A**gency for **M**edicines and **H**ealth **P**roducts
(FAMHP)

Regulator's view

A risk based approach - rationale and decision points

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Biosimilar Monoclonal Antibodies

Incorporation of comments under discussion

NC strategy: **A risk-based approach?**

A step-wise approach to identify potential risks which require further investigation on a case-by-case basis.

3 steps:

1. *In vitro* studies → fundamental in NC comparability
2. Identification of factors of importance for the evaluation of the need for *in vivo* studies
3. *In vivo* studies

Timing: **before** initiating clinical development

Comparative *In vitro* studies (step 1)

On an appropriate number of batches

- Binding to target antigen(s)
- Binding to closely related molecules

  (e.g. TNFβ for a mAb directed against TNFα)
- Binding to Fcγ receptors (FcγRI, FcγRIIA, FcγRIIB and FcγRIIIB)
  FcRn and complement (C1q)
- Fab-associated functions

  (e.g. neutralization, receptor activation or receptor blockade)
- Fc-associated functions (e.g. ADCC and CDC)

  No complement activation assay

No TCR studies: see ICHS6(R1)

Factors of importance for the evaluation of the need for *in vivo* studies (step 2)

Some mAbs may mediate effects that cannot be fully elucidated by *in vitro* studies.

→ **Relevant *in vivo* model?**

- species: NHP or transgenic animals or transplant models
- design: sensitivity and variability

Factors to consider if relevant *in vivo* model available:

- ➢ different cell expression system
- ➢ impurities that need to be characterized (product- and/or process related)
- ➢ differences in formulation (excipients not widely used for mAbs)

Factors of importance for the evaluation of the need for *in vivo* studies (step 2)

- If step 1 OK & no concern in step 2:

OR these do not block direct entrance into humans

(consider risk mitigation principles for FIM)

→ **NO in vivo animal study**

In vivo studies (step 3)

- If in vivo studies deemed necessary
  - Focus of study (PK and/or PD and/or safety) depends on need for additional information
  - Design : maximise the information obtained

    Non-terminal? → 3Rs
  - Conc-response assessment covering human therapeutic dose
  - Duration study → PK & clinical posology

In vivo studies (step 3)

- Comparative toxicology studies

  → not recommended

  (also not in non-relevant species)

- Immunogenicity: store blood samples

- Safety pharmacology, local tolerance, reproduction toxicology, mutagenicity and carcinogenicity studies

  → not required