

Fig. 8/1

Testing strategies according to the pre-determined immunogenicity risk

	<i>Low/medium risk biological</i>	<i>High risk biological</i>
<i>Preclinical Development (pivotal toxicity studies)</i>	Binding Antibodies Validated screening assay (99.9 <sup>th</sup> confidence interval)	Binding Antibodies Validated screening assay (99.9 <sup>th</sup> confidence interval)  Neutralizing Antibodies Validated competitive ligand binding assay for antagonists <i>or</i> Validated cell-based assay for agonists  and PD marker indicating potential neutralizing effects in GLP tox
<i>Phase I (FIM/FIP)</i>	Binding Antibodies Validated screening <u>and</u> confirmatory assay	Binding Antibodies Validated screening <u>and</u> confirmatory assay  Neutralizing Antibodies Validated competitive ligand binding assay for antagonists <i>or</i> Validated cell-based assay for agonists
<i>Phase II and later</i>	Binding Antibodies Validated screening and confirmatory assay  Neutralizing Antibodies To be discussed on a case by case basis with the authorities (primary concern: loss of efficacy, not safety)	Binding Antibodies Validated screening <u>and</u> confirmatory assay  Neutralizing Antibodies Validated competitive ligand binding assay for antagonists <i>or</i> Validated cell-based assay for agonists

According to Dr. B. Liedert, Oct. 2010

## Fig. 8/2

Testing strategies according to the pre-determined immunogenicity risk

Additional remarks:

- Based on the "*Guideline of Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins*" (EMA/CHMP/BMWP/14327/2006) any immunogenicity strategy will always have to be adapted individually for each project. Therefore, it is very important to discuss the proposed strategy with the authorities as early in development as possible
- The safety risks associated with medium risk proteins (hypersensitivity, overstimulation) cannot be covered with a bioanalytical strategy but have to be handled in a case-by-case manner, i.e. testing should include e.g. skin prick testing, Radio-Allergo-Sorbent Testing (RAST), as well as testing for PK and PD markers
- Sampling for immunogenicity testing should be based on the risk class:
  - For low and medium risk proteins, sampling should be more frequent early in drug development programs and less intensive in phase III trials
  - For high risk proteins, sampling should be intensive during all phases of clinical development

According to Dr. B. Liedert, Oct. 2010

## Disclaimer

The views expressed in this summary are the personal views of Dr. Bernd Liedert and may not be understood or quoted as being made on behalf of, or reflecting the position of Merck Serono.