Regulatory Aspects of the Safety Evaluation of MAbs in the US and in Europe

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Issues to be addressed

- D - Definition of MAbs
- G - Glimpse on Pre-clinical testing programme
- R - Regulatory Environment: Impact on Approval time?
- A - Analysis of EPARs: Does practice reflect theory?

Monoclonal Antibodies (mAbs)

- Homogeneous population of abs derived from a single cell, same specificity towards an epitope
- Murine>totally human mAbs
- Therapeutic indications: transplantation, cancer

Pre-clinical Testing: Studies to do

- In vitro cross-reactivity studies ←
- Single-dose pharmcokinetics
- Repeat-dose toxicity studies
- Immunogenicity studies
- Reproduction toxicology - in selected cases

Pre-clinical Testing: Studies not to do

- Conventional distribution, metabolism and excretion studies
- Genotoxicity studies
- Conventional 2-year carcinogenicity studies

Does Practice reflect Theory?

Analysis of European Public Assessment Reports

EPAR Analysis of MAbs

- Testing programme for mAbs is designed on a case-by-case basis
- Practice only partly reflects theory

EPAR Analysis of MAbs

	Daclizumab	Basiliximab
Type	IgG1	
Directed against	IL-2 receptor	
Indication	Renal allograft rejection	
In-vivo PD	+	-
Single dose	+	-
Repro.toxicity	-	+

EPAR Analysis of MAbs

	Daclizumab	Basiliximab	Infliximab
Mutagen. Genotox.	Ames test, Chrom. aberration test	Ames test, Chrom. aberration test	Complete test battery

→ Practice only partly reflects theory; Expectations from health authorities / Requests from ethic's committee

Approval time for Mabs: US vs EU

MAb	**Review time** (in months)	
	CBER	EMEA/EU-Com.
Basiliximab	6.0	18
Daclizumab	6.0	12
Trastuzumab	4.7	18
etc…		

→ **2-3 times longer** in EU compared to US; (priority review status in the US)

What to do?

- EU companies: familiarize with the US legislative / FDA philosophy
- EU companies: applications under ‘exceptional circumstances’
- Closely watch the modifications of the existing European legislation

Thank you

Approval time for Mabs: EU

	CPMP Active time	Applicant Clock-stop	EMEA Commission
Basiliximab **Daclizumab** **Trastuzumab** **etc…**	**~ 6** months	**3 - 10** months	**~ 3** months

→ Regulatory Environment impacts on approval time