Evaluating optimal study designs for toxicity studies with monoclonal antibodies: results from a MEB/Industry/NC3Rs survey

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INTRODUCTION

- Non-clinical development of monoclonal antibodies (mAbs) is guided by ICH S6(R1), which allows a flexible approach.
- Typically, packages of studies consist of First-in-Human (FIH)-enabling studies (~1-month) in pharmacologically-relevant rodent and/or non-rodent species to support early developmental phase and a chronic study (to 6 months) in at least one species to support later developmental phase.
- Previous initiatives have focused on optimizing the duration and design of chronic toxicity studies for biopharmaceuticals [1,2] and whether 6-month studies are needed [1, 2, 3, 4].

PROJECT AIM

- Re-evaluate the need for chronic repeat-dose toxicity studies with mAbs.
- Develop a science-driven framework for optimal study designs and duration.

SURVEY & ANALYSIS

A survey containing 3 main sections was conducted:
- Basic product information (species selection, pharmacological relevance); individual study data; short- and longer-term study comparisons.
- Data collection from March-December 2020.

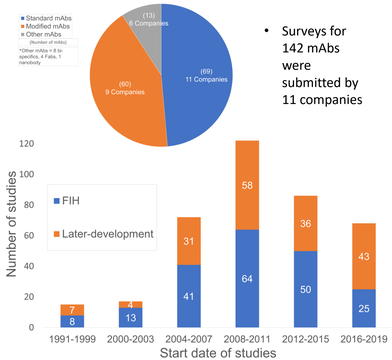
Analysis focused on:
- Species used, pharmacological relevance, study designs for short-term and chronic studies.
- How often were novel adverse events identified in chronic studies; did novel adverse events alter clinical development; could a 3-month study have been sufficient to support further clinical development?

REFERENCES

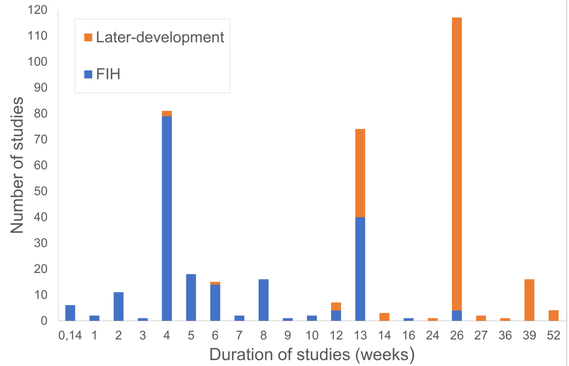
(1) Clarke *et al.* (2008). Duration of chronic toxicity studies for biotechnology-derived pharmaceuticals: Is 6 months still appropriate? *Regulatory Toxicology & Pharmacology.* 50: 2 – 22. (2) Chapman *et al.* (2012). The design of chronic toxicology studies of monoclonal antibodies: Implications for the reduction in use of non-human primates. *Regulatory Toxicology & Pharmacology.* 62: 347 – 354. (3) Blaich *et al.* (2016). Non-clinical Safety Evaluation of Biotherapeutics e Challenges, Opportunities and new Insights. *Regulatory Toxicology & Pharmacology.* 80: S1 – S14. (4) Sewell *et al.* (2017). Challenges and opportunities for the future of monoclonal antibody development: Improving safety assessment and reducing animal use. *Mabs.* 9(5):742-755.

RESULTS

Overview of dataset



- Surveys for 142 mAbs were submitted by 11 companies
- 59%:41% of studies were conducted pre- or post-ICH S6(R1) revision.



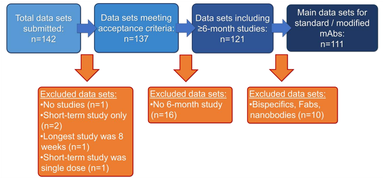
- High variability in study duration (1 day to 13 weeks for FIH-enabling studies; 13 to 52 weeks for studies to support later development)

Pharmacological relevance, species used and group sizes

Group size used in shortest study		Difference in animal use from shortest to longest study		
		Same	Increased	Decreased
2 M + 2 F:	1 mAb		1	
3 M + 3 F:	112 mAbs	42	54	16
4 M + 4 F:	16 mAbs	9	3	4
5 M + 5 F:	1 mAb			1
Other – variable:	2 mAbs	1		1

- 44% of mAb studies maintained the same group size, but 54% increased group sizes between the studies.

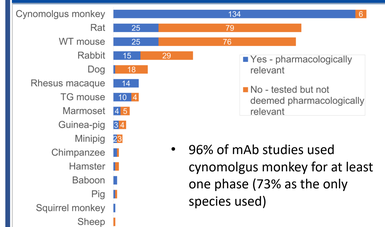
Data inclusion / exclusion



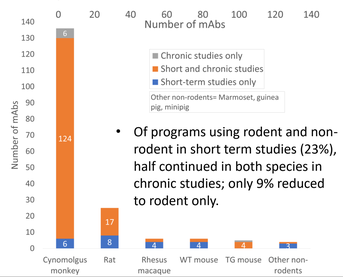
- 111 standard or modified mAb data sets were used for the analysis of rate of new toxicities*

*New toxicity is defined as an adverse finding only observed in chronic studies.

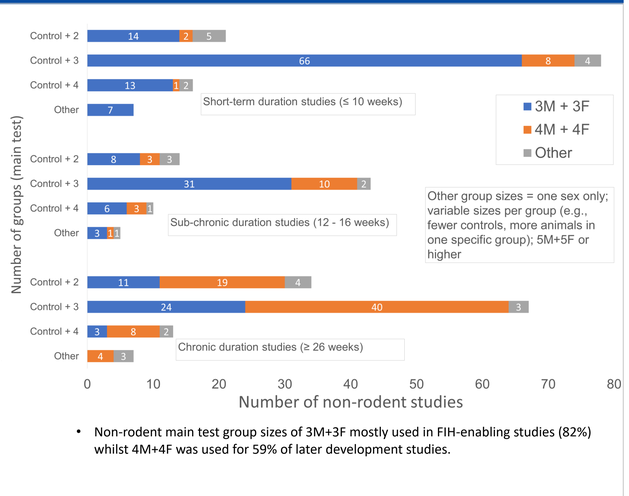
Pharmacological relevance, species used and group sizes



- 96% of mAb studies used cynomolgus monkey for at least one phase (73% as the only species used)

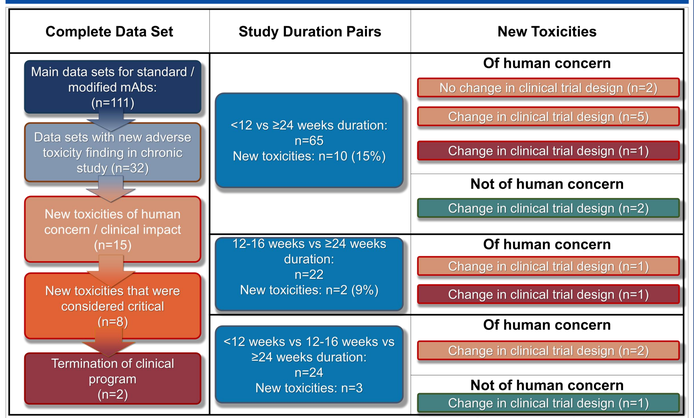


- Of programs using rodent and non-rodent in short term studies (23%), half continued in both species in chronic studies; only 9% reduced to rodent only.



- Non-rodent main test group sizes of 3M+3F mostly used in FIH-enabling studies (82%) whilst 4M+4F was used for 59% of later development studies.

Rate of new toxicities; Risk perception



- In **79/111 (71%)** no toxicities or no new toxicities were noted. For **only 2 mAbs (2%)** were the new toxicities observed in chronic studies considered sufficient to terminate the clinical program.
- The rate of new toxicities observed in chronic studies decreased from 17% to 12.5% to 9% when the duration of shorter-term studies increased from ≤ 4 weeks to 5 –11 weeks to 12 –16 weeks, respectively.

DISCUSSION

- "More mAb programs could follow ICHS6(R1) guidance around using 1 pharmacologically responsive species for later development studies."
- "Increasing group size for chronic studies is not necessary; two test article-dosed groups are often acceptable"
- "For the majority of mAbs (71%) in the dataset, no new findings were identified in chronic studies."
- "Although 15 mAbs (13.5%) had new toxicities of concern, 8/15 new toxicities were considered critical, and only 2/8 resulted in termination."
- "Three-month studies may be more informative compared to one-month studies to support FIH clinical trials."

CONCLUSION

- "The high variability in study design and group size likely reflects case-by-case approaches as outlined in ICHS6(R1) and demonstrates more opportunities to optimize non-clinical packages for some mAbs."
- **"For consideration, a weight-of-evidence approach and a study of 3 months duration may derisk certain mAbs. Further work is ongoing to develop this and will be described in a manuscript in preparation."**

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