Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies, using a weight-of-evidence approach

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INTRODUCTION

- Non-clinical development of monoclonal antibodies (mAbs) is guided by ICH S6(R1), which allows a flexible approach.
- Typically, a mAb toxicology program of studies consists of First-in-Human (FIH)-enabling studies (1- to 3-month) in pharmacologically-relevant rodent and/or non-rodent species to support early developmental phase and a chronic study (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 the need for 6-month studies [(1,2,3,4)].

PROJECT AIM

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

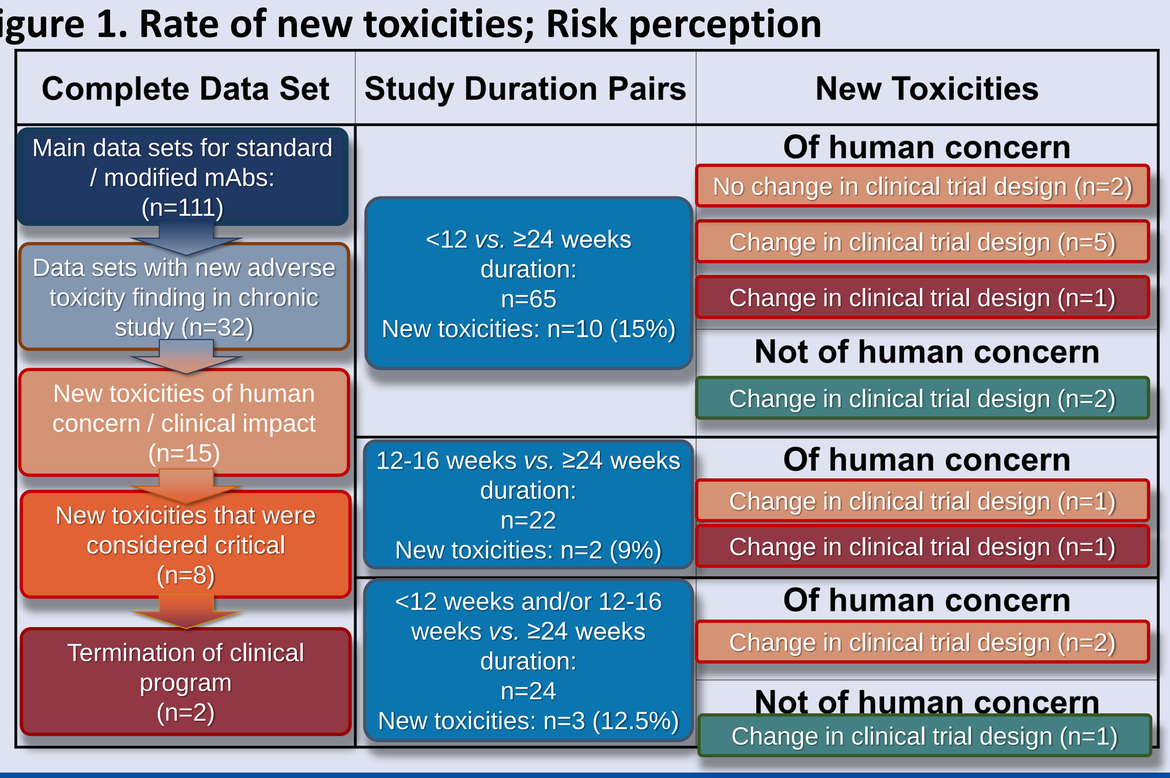
SURVEY & ANALYSIS

- A survey was conducted for toxicology studies performed between 1991 and 2019, requesting key information on the molecule, species selection and pharmacological relevance, short- and longer-term/chronic study data.
- Analyses focused on how often novel adverse events were identified in chronic studies; if novel adverse events altered clinical development; and could a 3-month study have been sufficient to support longer-term clinical development and registration/marketing authorization?

RESULTS

- Data sets from 142 mAbs were submitted by 11 companies.
- 59% *vs.* 41% of studies were conducted pre- vs. post ICHS6(R1) revision
- 111 standard or modified mAb data sets were used to analyze the rate of new toxicities (defined as an adverse finding only observed in longer-term/chronic studies; Figure 1).
- In 79/111 (71%) no toxicities or no new toxicities were noted. For only 2 mAbs (2%) the new toxicities observed in longer-term/chronic studies were considered sufficient to terminate the clinical program (Figure 1).

Figure 1. Rate of new toxicities; Risk perception



USE OF WEIGHT-OF-EVIDENCE (WoE) MODEL

- Consideration of available data using the sliding component of the weight-of-evidence (WoE) model (Figure 2) informs the degree of risk for each question in a final flow model (Figure 3) to determine whether a chronic study is likely to be required.
- The WoE model is intended to be used in an iterative manner throughout early development and revisited as additional nonclinical or clinical toxicity data become available to inform a final decision.

CONCLUSION

- In retrospect, only a small proportion of chronic studies provided additional safety findings relevant to clinic.
- To guide the need for chronic toxicity studies, an iterative WoE model was developed, which considers factors that influence the overall risk. This model drives the selection of the optimal duration of toxicity studies, and based on the experience of this WoE approach, we believe many programs will not need a 6-month study.
- This provides a science-based approach that may enable chronic studies to be waived in some circumstances whilst still ensuring human safety.

REFERENCES

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WEIGHT-OF-EVIDENCE (WoE) MODEL

Figure 2. Sliding section

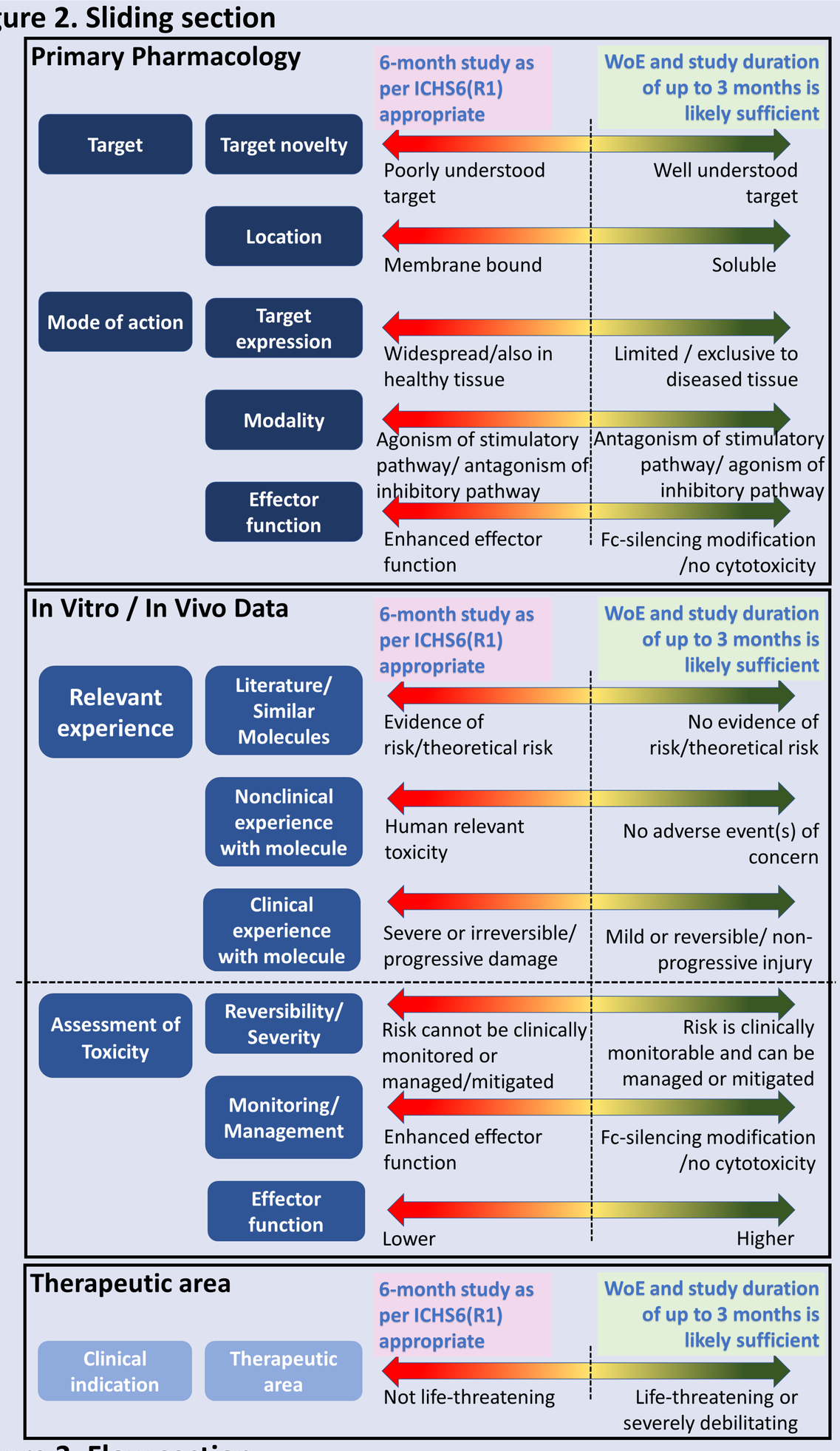
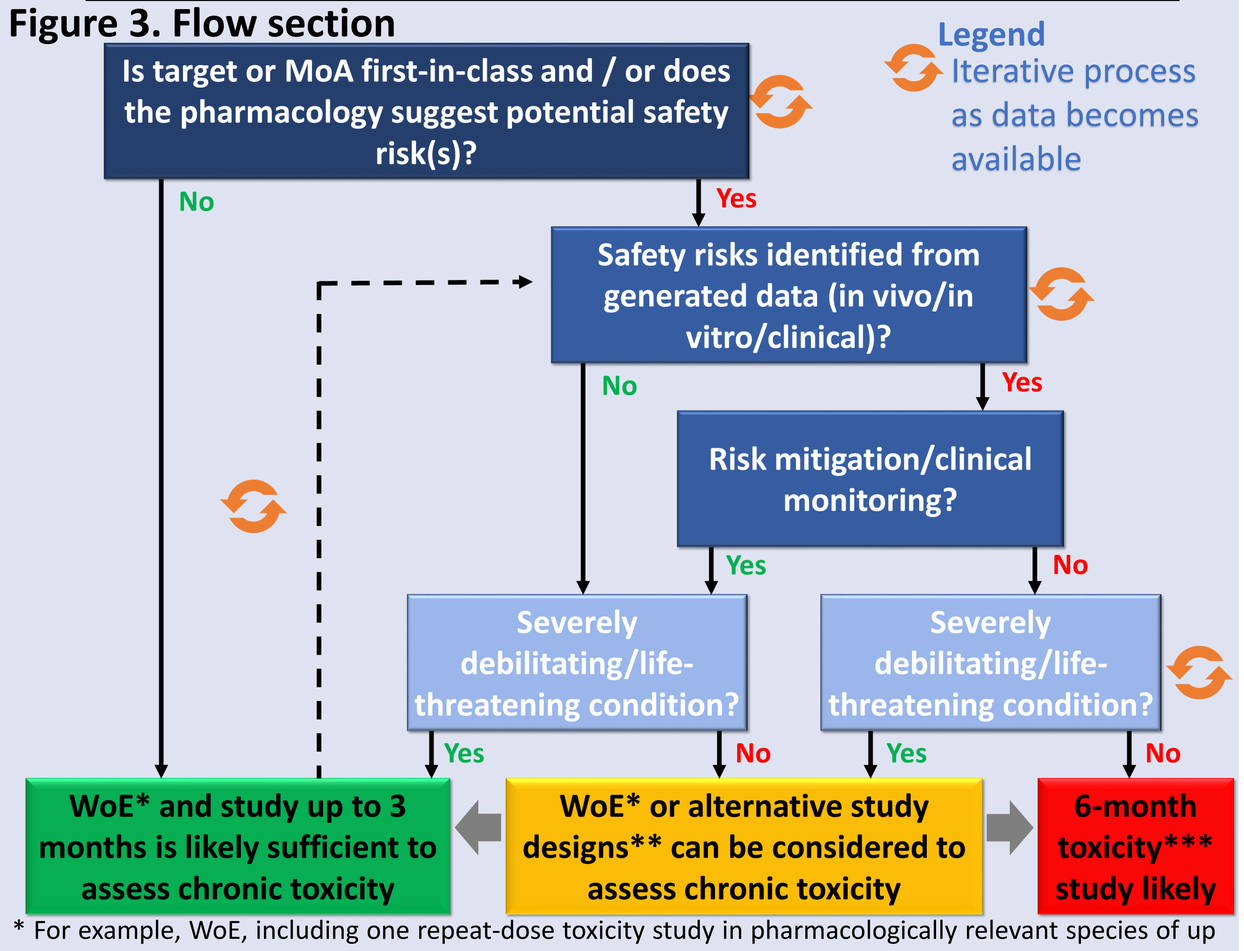


Figure 3. Flow section



* For example, WoE, including one repeat-dose toxicity study in pharmacologically relevant species of up to 12 weeks duration, to support clinical development; ** Examples of alternative study designs include optimized for animal usage, refined dosing duration; *** Optimized for animal usage, recommendations on optimal study designs to be included in the manuscript

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