Approaching Non-Animal Preclinical Safety Testing for Pharmaceuticals

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Problem Statement

How best to shift preclinical testing… **from defaulting to animal tests…** **to using the most human-relevant methods available?**

We propose **two parallel paths** to leverage case study successes into formal guidance replacing drug class-specific preclinical animal use:

Path 1: Immuno-Oncology

Step 1: Identify published case studies where immuno-oncology drug developers used non-animal preclinical data to support human clinical trials

2011 — “**No pharmacologically relevant animal species exists for testing the toxicity** of MEDI-565… Rather, MedImmune implemented a strategy that utilized an *in vitro* approach to assess nonclinical safety instead of performing *in vivo* toxicity studies[4].”

MedImmune / Amgen’s MEDI-565 US clinical trial completed in 2015

2016 — “…**neither of the previous approaches** [surrogate, double-transgenic mice] **provided a suitable and pharmacologically relevant model** to assess the safety of CEA TCB[5].”

Several of Roche’s global CEA TCB clinical trials had been completed by 2020

2018 — “**Animal models are not deemed suitable for ImmTAC testing** for a number of reasons… We propose that this entirely *in vitro* preclinical assessment package represents a potential paradigm shift in the approach to preclinical assessment of TCR-based therapies by providing a more physiologically relevant substitute for traditional *in vivo* preclinical testing[1].”

Immunocore’s KIMMTRAK® was approved in the EU, the US, and the UK in 2022

2019 — “The treatment ‘just doesn’t lend itself to the use of animal models’…[2] *[I]**n vivo* **animal studies** were unlikely to provide any additional understanding of the safety profile of ATL001 and were not required and, indeed, **were discouraged [by MHRA]**[3].”

Achilles’ ATL001 clinical trials were underway in the US and UK by 2019

2020 — “The peptide-specific nature of these responses **makes *in vivo* toxicology studies unsuitable**… We developed an extensive *in vitro* preclinical testing protocol to evaluate the safety and efficacy of SPEAR T-cell therapies[6].”

Several of Adaptimmune’s global ADP-A24M clinical trials were underway by 2017

Built off retrospective learnings from a previous similar program that unexpectedly caused two human fatalities in the clinic, and warned in a publication[7] that animal tests are “unlikely to be suitable for predicting toxicity” of drugs in that class

Step 2: Propose regulatory guidance on non-animal preclinical in the immuno-oncology space

Developers do not have formal regulatory guidance to reference as a rationale when asserting in regulatory submissions that immuno-oncology candidate therapeutics are best de-risked with a preclinical protocol that does not include animal tests…

…which can lead to negative outcomes, for example:

- New animal data collected but not used for decision-making
- Time and money lost on unsuccessful surrogates and modified animal tests
- Serious human adverse events in the clinic

Call to Action

Immuno-oncology stakeholders and global regulators must collaborate to address this need for guidance via:

- Consortium of pharma stakeholders
- Workshops
- Targeted meetings

Path 1 Conclusion:

When developers and regulators agree that animal tests are inadequate for predicting the human response of an immuno-oncology drug candidate, they rely on non-animal, human-relevant methods.

We can extend this consideration to <u>all</u> new drug candidates.

Path 2: Monoclonal Antibodies against Foreign Antigens

Step 1: Develop a case study for non-animal preclinical with a drug candidate <u>outside</u> the immuno-oncology space

Target Drug Class: Purified human recombinant monoclonal antibody therapeutic directed against a foreign antigen

Case Study Candidate Therapeutic: Purified human recombinant monoclonal antibody therapeutic directed against diphtheria toxin for the treatment of diphtheria[8]

Why this class?

- Class Has Low Risk Safety Profile
- ICH Guidance Supports Drug Class-Specific Tox Testing
- Class is Well-Understood
- Well-Developed Human Cell / Tissue Assays Available to Evaluate Risks
- Animal Tests are Poor Predictors of Class’ Risks

FDA Pre-IND Meeting, May 2022
- Non-animal preclinical weight of evidence (WoE) approach “appears reasonable”
- Agency welcomes further communication prior to IND submission

EMA Scientific Advice, May 2023
- “…animal studies are of limited informative value” for the case study therapeutic
- “…could be acceptable to proceed to a FIH clinical trial in the absence of animal toxicity data…”

EMA Innovation Task Force, Oct 2023
- WoE approach is “scientifically justified”, could be formally defined in the future if more data collected
- WoE approach is fit for broader industry discussion, workshops supporting its broader implementation, and may be appropriate for inclusion in EMA 3Rs Working Party work plan

PEI Scientific Advice, Apr 2024
- Agreement with EMA outcomes
- WoE confidence may be supplemented with additional in vitro tissue cross-reactivity data to bolster conclusion of low risk

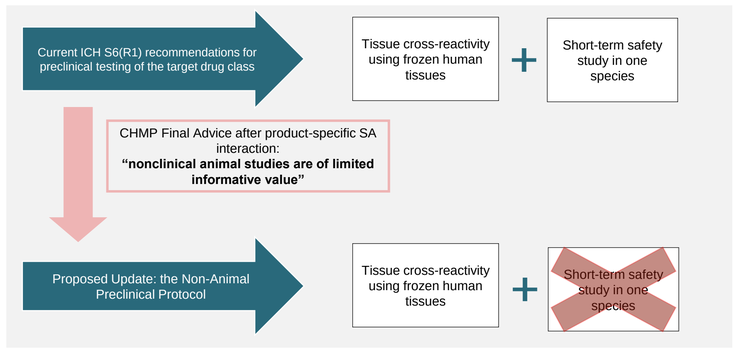
Call to Action

Pharmaceutical stakeholders and global regulators must be clear about situations when animal data will not be considered useful for decision-making <u>before</u> developers collect it

- Retrospective reviews by regulators and developers
- Data sharing & consensus-building
- Timely updates to existing guidance

Step 2: Expand non-animal preclinical to any new drug in the same class as the case study candidate

Broaden EMA product-specific Scientific Advice from Step 1 to other new therapies in the same class by defining a non-animal preclinical protocol



Defined: the Non-Animal Preclinical Protocol

- Removes an animal study when it is of limited informative value for a specific drug class
- **Context of use**: Preclinical safety evaluation (before a first-in-human clinical trial) of <u>purified human recombinant monoclonal antibody therapeutics directed against foreign targets</u>
- **Considerations for risk management**:
  - Additional toxicity assessment may be appropriate if the cross-reactivity study indicates an unacceptable level of risk
  - A cautious clinical development strategy must be implemented, with a low starting dose and cautious dose escalation
  - Human immunogenicity should be evaluated within clinical trials
  - Developers must justify the absence of unexpected product-specific toxicity that may not be addressed by a cross-reactivity study

Path 2 Conclusion:

Regulators broadly agree that a currently-required safety study using animals is of limited informative value in the context of a case study candidate therapeutic, and the candidate can be appropriately de-risked using exclusively non-animal methods. We can extend this consideration to similar drugs, and eventually to all new drugs.

References

[1]Harper, J et al. (2018). An approved in vitro approach to preclinical safety and efficacy evaluation of engineered T cell receptor anti-CD3 bispecific (ImmTAC) molecules. *PLoS ONE*, *13*(10), 1–19.; [2]Brizmohun, N. (2019). Achilles on getting “new wave” immunotherapy from concept to clinic in three years. *Pink Sheet*, 1–5.; [3]Jones, D R. (2022). A Regulatory Perspective of “New Approach Methodologies (NAMs).” Increasing confidence in NAMs for regulatory decision-making (NC3Rs webinar). S5: Acceptance of NAMs in the regulation of pharmaceuticals – what are the challenges and how they can be overcome.; [4]Ryan, P C et al. (2011). In Vitro MABEL Approach for Nonclinical Safety Assessment of MEDI-565 (MT111). *Altex Proceedings*, 85–87.; [5]Dudal, S et al. (2016). Application of a MABEL Approach for T-Cell-Bispecific Monoclonal Antibody: CEA TCB. *Journal of Immunotherapy*, *39*(7), 279–289.; [6]Sanderson, J P et al. (2020). Preclinical evaluation of an affinaity-enhanced MAGE-A4-specific T-cell receptor for adoptive T-cell therapy. *OncoImmunology*, *9*(1), e1682381-1–e1682381-11.; [7]Cameron, B J et al. (2013). Identification of a Titin-Derived HLA-A1-Presented Peptide as a Cross-Reactive Target for Engineered MAGE A3-Directed T Cells. *Science Translational Medicine*, *5*(197), 1–24.; [8]Wenzel, E V et al. (2020). Human antibodies neutralizing diphtheria toxin in vitro and in vivo. *Scientific Reports*, *10*(571), 1–21.