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PMDA's initiatives and thoughts for 3Rs and NAMs

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Today’s talks

- PMDA’s initiatives to date for 3Rs and NAMs
- PMDA’s future initiatives for 3Rs and NAMs
- PMDA’s thoughts on the FDA Announcement/Roadmap
- Examples of successful reduction or elimination of animal testing
- Summary

This presentation is based on the personal views of the presenter and does not represent the official views of Pharmaceuticals and Medical Devices Agency

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PMDA's initiatives to date for 3Rs and NAMs

Past

PMDA is committed to promoting the 3Rs and NAMs and contributing to them through domestic and international activities.

- ICH activities: S5(R3), E14/S7B QA, S1B(R1), etc.
- International activities: collaboration with IWG3R, participation in FNIH NAMs-VQN, et al
- Domestic activities: participation in AMED research group involving in NAMs and JaCVAM

Present

Internal research

AMED research group
- Internal group for ICH
- Alternative methods/MPS

MHLW research group
NAMs

Collaboration with JaCVAM
Validation of Alternative Methods

ICH
Global discussion

Global discussion

HESI DART & Immuno-Safety Technical committee
NAMs/Alternative group

IQ MPS affiliate
Discussion about MPS per organ

FNIH NAMs-VQN

IMRWG3Rs
Global discussion

PMDA's future initiatives for 3Rs and NAMs

Present

PMDA is committed to promoting the 3Rs and NAMs and contributing to them through domestic and international activities.

Future

PMDA will review current frameworks and disease areas to identify animal testing that can be reduced.

In parallel, PMDA will consider establishing a qualification system for NAMs as part of its efforts to promote NAMs in Japan.

PMDA will also focus on improving the understanding and education of regulatory review staff.

Promoting NAMs in Japan

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PMDA's thoughts on the FDA Announcement/Roadmap

- PMDA's thoughts is outlined below:

  ✓ Focus Firstly on Monoclonal Antibodies

  Supports FDA’s approach to eliminate long-term repeated-dose toxicity studies in NHPs and shorten dosing period when no safety concerns in the 1-month study and NAM study.

  ✓ Need for International Consensus

  Believes revision of the ICH S6(R1) is essential, as this approach will change the current framework for nonclinical safety evaluation of monoclonal antibodies.

  ✓ Collaboration with FDA

  Intends to work together to propose topics for updating ICH S6(R1) guideline

PMDA's thoughts on the FDA Announcement/Roadmap

- PMDA's thoughts is outlined below (continued):

FDA has stated that it will also make exceptions for drug development involving small molecule compounds in the future.

✓ Be Cautious About Expanding to Small Molecules

- Modalities such as small molecules have concerns about off-target toxicity
- Repeated-dose toxicity studies are very important studies, because they are directly related to human safety and are also a WoE element for omitting rat carcinogenicity studies based on the S1B(R1) guideline.
- In Japan, regulatory agencies bear significant responsibility for drug-related adverse events

Examples of successful reduction of animal testing

Symposia Review

Alternatives to Monkey Reproductive Toxicology Testing for Biotherapeutics

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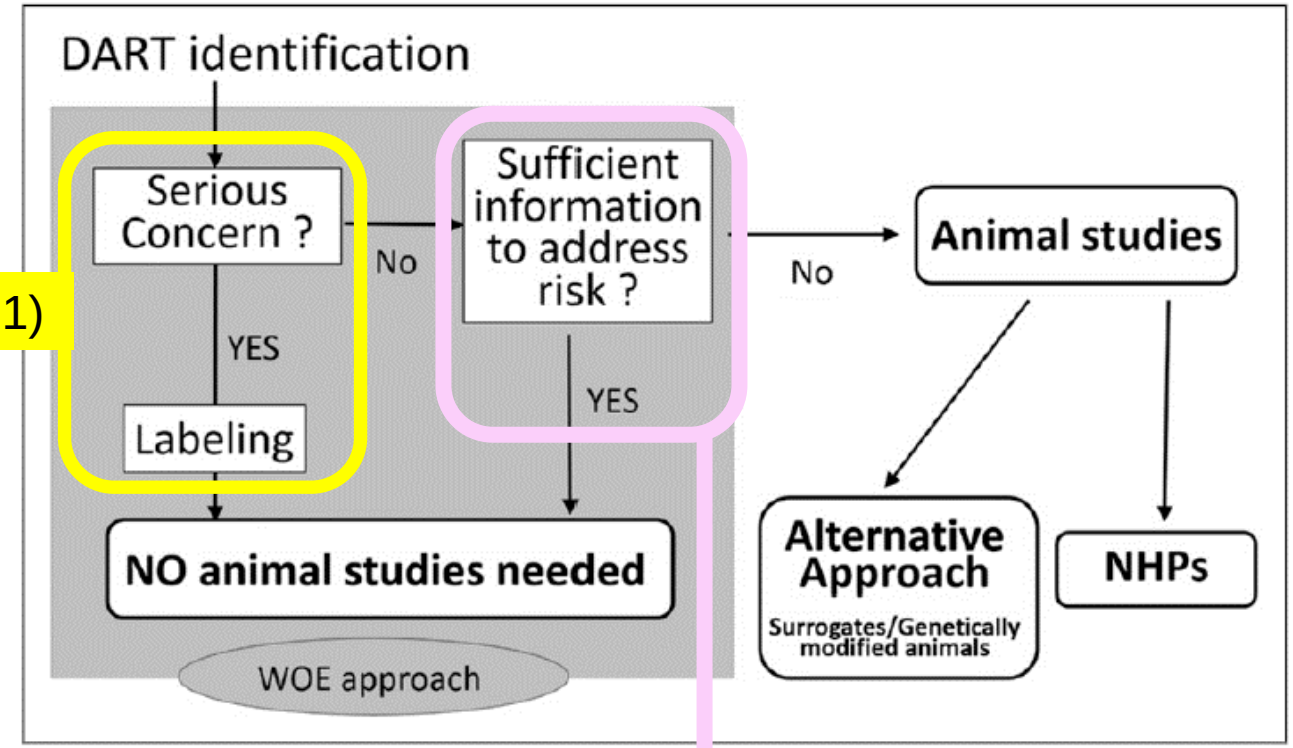
Abstract

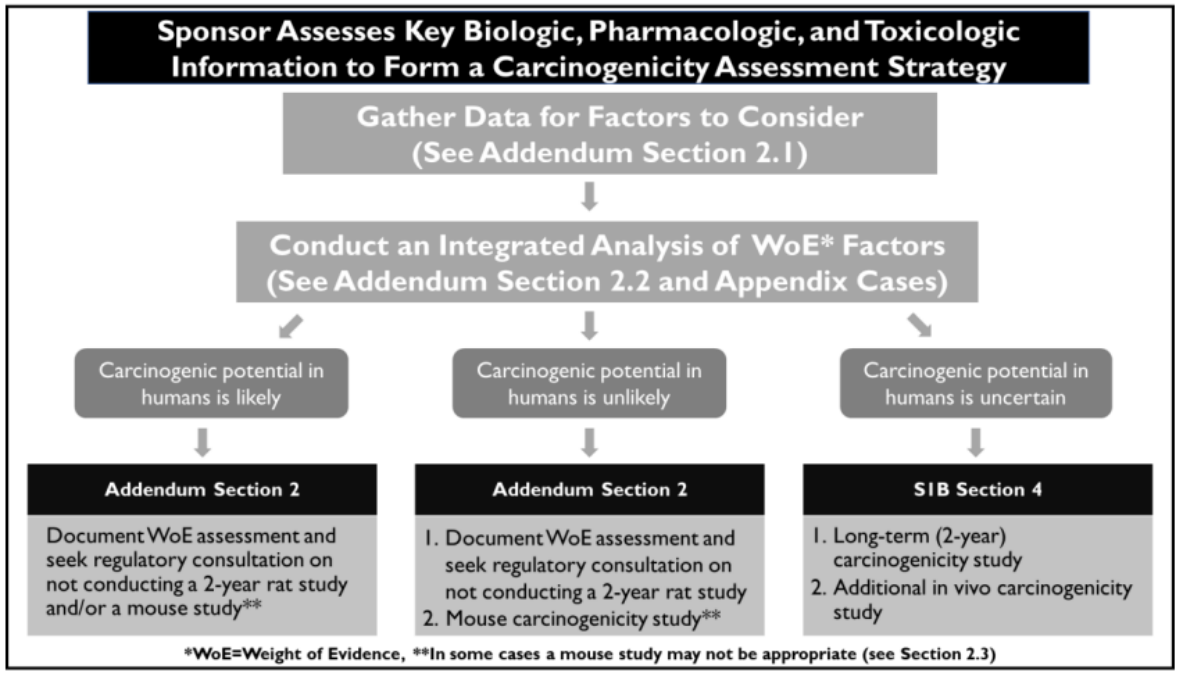
Embryofetal toxicity studies are conducted to support inclusion of women of childbearing potential in clinical trials and to support labeling for the marketed pharmaceutical product. For biopharmaceuticals, which frequently lack activity in the rodent or rabbit, the nonhuman primate is the standard model to evaluate embryofetal toxicity. These studies have become increasingly challenging to conduct due to the small number of facilities capable of performing them and a shortage of sexually mature monkeys. The low number of animals per group and the high rate of spontaneous abortion in cynomolgus monkeys further complicate interpretation of the data. Recent FDA guidance has proposed a weight of evidence (WoE) approach to support product labeling for reproductive toxicity of products intended to be used for the treatment of cancer (*Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*), an approach that has also supported the approval of biotherapeutics for non-cancer indications. Considerations to determine the appropriateness and content of a WoE approach to support product labeling for embryofetal risk include known class effects in humans; findings from genetically modified animals with or without drug administration; information from surrogate compounds; literature-based assessments about the developmental role of the pharmaceutical target; and the anticipated exposure during embryofetal development. This paper summarizes the content of a session presented at the 42nd annual meeting at the American College of Toxicology, which explored the conditions under which alternative approaches may be appropriate to support product labeling for reproductive risk, and how sponsors can best justify the use of this approach.

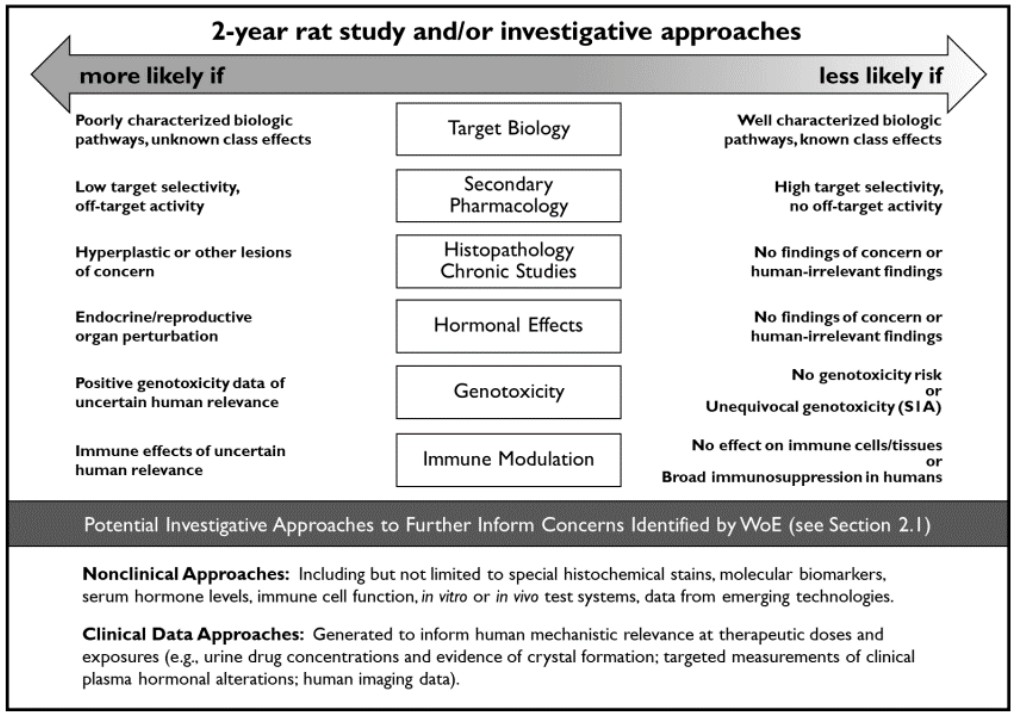
ICH S6(R1)



This paper proposes a strategy to allow exemption of reproductive and developmental toxicity studies in monkeys based on a WoE evaluation that is not covered by ICH S6(R1).
WoE factors are the below; known class effects in humans, knowledge gained from genetically modified animals with and without drug administration, information gained from alternative compounds, a literature-based evaluation of the developmental role of the drug target, and expected exposure during embryo-fetal development

Examples of successful reduction or elimination of animal testing





- The exemption from rat carcinogenicity testing based on the ICH S1B(R1) guideline is an example of a significant contribution to reducing rat carcinogenicity testing based on WoE assessment.
- The decision on whether or not to exempt is made by each regulatory authority, so there is a fair amount of disagreement in judgment, which was shared at the ICH S1B(R1) regulatory authority (five countries) meeting.
- The process of the decision is shared and used as a lesson for the future.

A successful example of off-target toxicity evaluation for antibody products for which in vitro tissue cross-reactivity study is not possible

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REVIEW

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The emergence of cell-based protein arrays to test for polyspecific off-target binding of antibody therapeutics

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ABSTRACT

Specificity profiling is a requirement for monoclonal antibodies (mAbs) and antibody-directed biotherapeutics such as CAR-T cells prior to initiating human trials. However, traditional approaches to assess the specificity of mAbs, primarily tissue cross-reactivity studies, have been unreliable, leading to off-target binding going undetected. Here, we review the emergence of cell-based protein arrays as an alternative and improved assessment of mAb specificity. Cell-based protein arrays assess binding across the full human membrane proteome, ~6,000 membrane proteins each individually expressed in their native structural configuration within live or unfixed cells. Our own profiling indicates a surprisingly high off-target rate across the industry, with 33% of lead candidates displaying off-target binding. Moreover, about 20% of therapeutic mAbs in clinical development and currently on the market display off-target binding. Case studies and off-target rates at different phases of biotherapeutic drug approval suggest that off-target binding is likely a major cause of adverse events and drug attrition.

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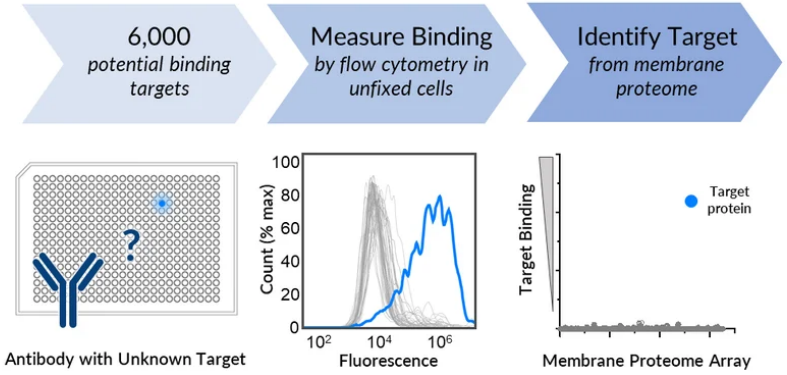
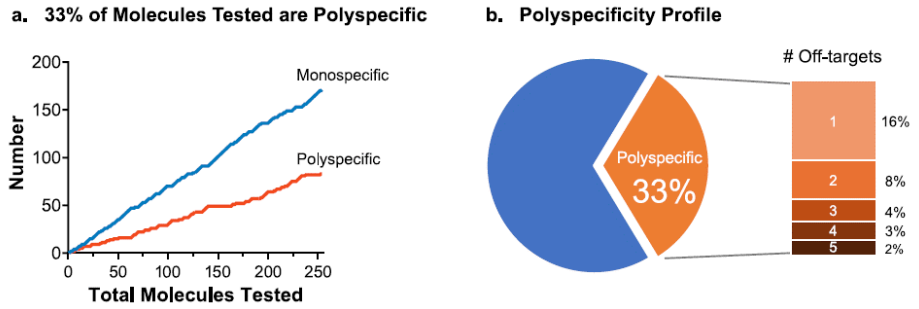
https://pmc.ncbi.nlm.nih.gov/articles/PMC11346545/pdf/KMAB_16_2393785.pdf





DDT Project Number	DDT Project Name	Latest Submission Stage and Stat	Organization Name	Document Type	Date	FDA Determination
DDT-IST-000006	Specificity Screening of Biotherapeutics for Improved Safety Profiling in IND Applications Using the Membrane Proteome Array (MPA)	QP - Qualification Plan -- Accept	Integral Molecular, Inc.	QP Determination Letter QP Executive Summary LOI Determination Letter LOI Submission	2025-01-08 2023-08-13 2022-07-01 2021-05-17	Accept N/A Accept N/A

https://force-dsc.my.site.com/ddt/s/

Summary

- Supports focus firstly on monoclonal antibodies
- Be cautious about expanding to small molecules due to concerns about off-target toxicity
- Believes that international (e.g. ICH) discussions are needed to discuss changes to the current framework utilizing the NAM.
- Intends to work to promote the 3Rs, with a view to revising the current ICH guidelines.

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