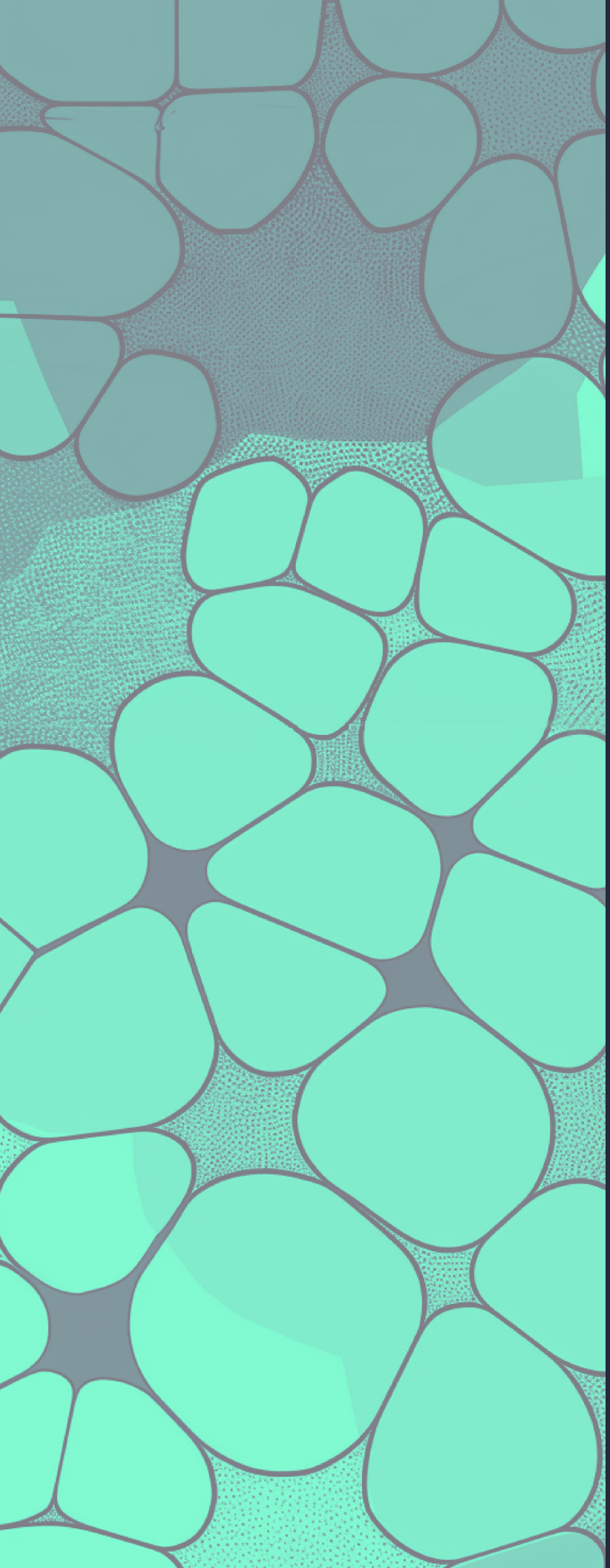

Guide

A Guide to the FDA Announcement to Phase Out Animal Testing for Drugs

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Executive Summary

The FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies has ushered in a new era of drug development—one where animal testing is no longer mandatory before conducting clinical trials. This announcement encourages pharmaceutical companies to adopt advanced, ethical, and scientifically robust alternatives, such as biosimulation, microphysiological systems (MPS), and in vitro platforms. This guide explains the implications of the FDA's roadmap to phase out animal testing, how global regulatory agencies are responding, and how the pharmaceutical industry can adapt to the transition by using Certara's Non-Animal Navigator™.

The next era in preclinical drug development

The FDA Modernization Act 2.0 replaced outdated requirements for animal testing, providing the flexibility to use computer modeling, in vitro data, and other validated New Approach Methodologies (NAMs) to demonstrate drug safety and efficacy. Drug developers now have a choice—to integrate these modern methods early, accelerating innovation while improving translational accuracy.

Global precedents for minimizing animal testing

- The EU has banned animal testing for finished cosmetic products and prohibits marketing cosmetics tested on animals under its cosmetics regulation. However, other regulatory regimes (e.g. under REACH) may still require animal tests for substances used in cosmetics in certain risk assessments (Figure 1).
- In the U.S., the FDA does not require animal testing in the cosmetic industry and does not prohibit it. Instead, it supports and encourages validated alternative approaches when available.
- In 2019, the U.S. EPA issued a directive aiming to reduce requests for mammal studies of chemicals by 30% by 2025 and eliminate them by 2035. The agency has since made ongoing efforts under the Toxic Substances Control Act (TSCA) and NAMs planning to reduce vertebrate animal testing of chemicals.
- The EMA actively supports the use and regulatory acceptance of alternative testing methods (NAMs) in drug safety assessments, promoting reduction and replacement of animal testing in medicinal development.

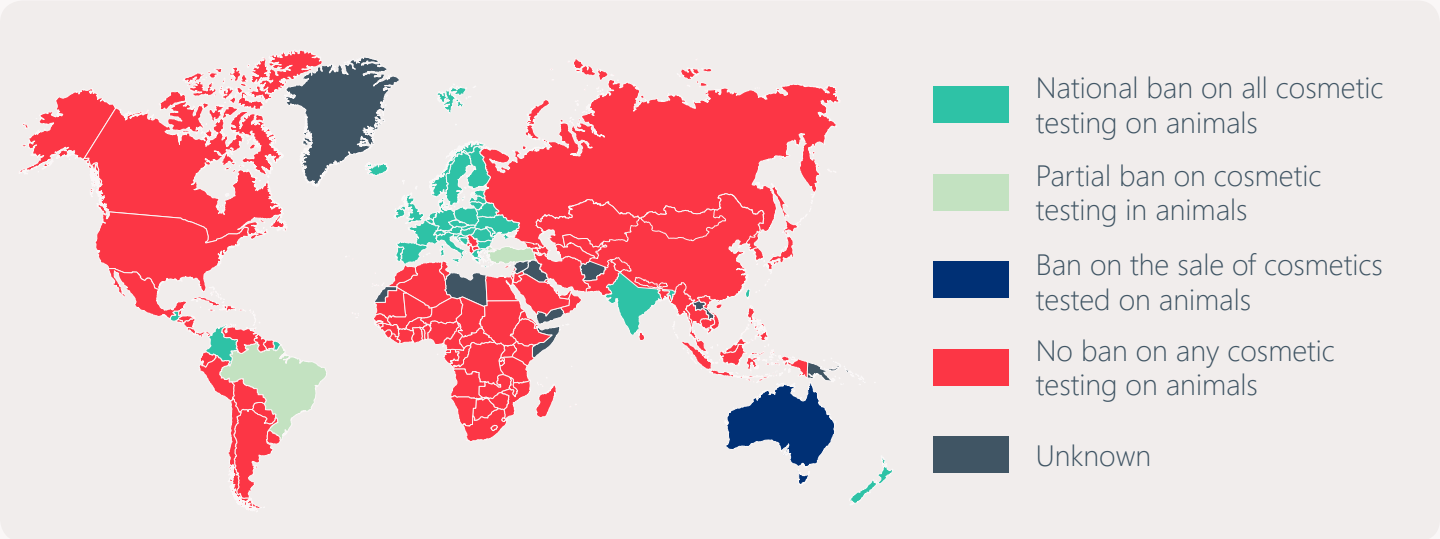


Figure 1. There has been a global push to reduce animal testing in the cosmetics industry

Why change is needed: the limits of animal testing of pharmaceuticals

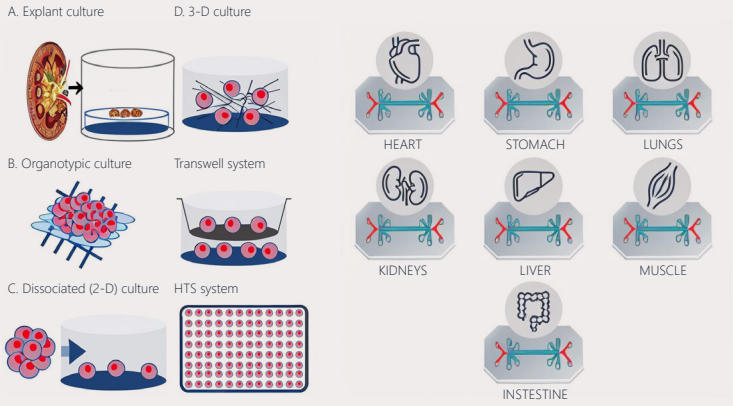
Over 90% of drugs that pass preclinical animal studies fail in human trials. The FDA's initiative targets these gaps, emphasizing the need for human-relevant models.

Computer-based models can simulate drug absorption, distribution, metabolism, excretion (ADME), off-target effects, and immunogenicity (when a therapeutic causes an immune response).

NAMs are more human-relevant, non-animal studies that fall into four main categories (Figure 2):

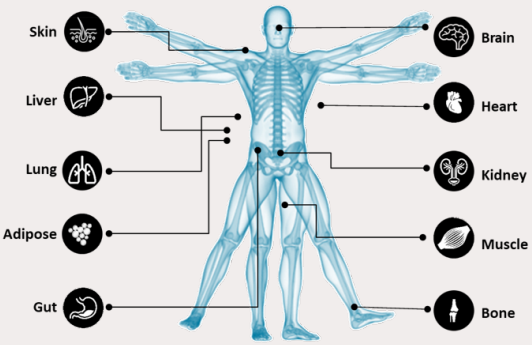
- **Microphysiological systems (MPS):** 2D/3D cultures and organ- or organoid-on-chip platforms that mimic human tissue function.
- **Advanced in vitro assays using human tissues:** Tools such as cytokine-release and T-cell activation panels to assess immunotoxicity.
- **Advanced ex vivo human systems:** Including tissue culture and pluripotent stem cells for high-throughput safety screening.
- **In silico tools:** Computer-based models that simulate drug absorption, distribution, metabolism, excretion (ADME), off-target effects, and immunogenicity (when a therapeutic causes an immune response). Physiologically-based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) models are frequently used as NAMs.

In Vitro Human Systems e.g. Organs-On-Chips



In vitro techniques established in many areas:
ADME > PD/efficacy > toxicity
Organ-on-a-chip technology is emerging

AI-Driven Modeling & Simulation



Established models include:
PBPK, QSP (pharmacology/efficacy/MABEL)
and Immunogenicity/Toxicity models

Figure 2. Alternatives to Reduce, Refine & Replace Animal Testing

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Monoclonal antibodies are leading the way in eliminating animal testing

The FDA's eventual goal is to eliminate animal testing for all drugs, but the FDA Roadmap prioritizes reducing non-human primate testing for monoclonal antibodies (mAbs). The nonclinical testing of mAbs presents unique challenges due to their precise target specificity, which often means there are no suitable non-human species for study, or NHPs may be the sole viable option. The average mAb program uses 144 NHPs at $50K each.

How biosimulation accelerates the transition away from animal tests

Biosimulation supports the 3Rs—Replacement, Reduction, and Refinement—by simulating human responses to therapies, reducing animal use, and refining experimental designs. Certara offers multiple platforms supporting the transition to non-animal testing models. Certara's Simcyp® PBPK Simulator enables predictive modeling for safety and efficacy. For example, this approach can be used to predict what dose to take into the clinic for first-in-human (FIH) studies (Figure 3).

Physiologically based pharmacokinetic (PBPK) models, such as those used in the Simcyp Simulator, are mechanistic models that represent human organs, blood flows, and relevant metabolic enzymes and transporters to simulate a drug's ADME. The first step is to feed in-vitro drug data such as molecular weight, target binding affinities, permeability, etc into the PBPK framework. The platform then creates virtual individuals/populations using human physiological parameters. The second step is to run PK/PD simulations in relevant human tissues to predict plasma and tissue concentrations, target engagement, and time courses. These simulations enable drug developers to identify dose levels that achieve desired PK/PD endpoints.

These predictions can be made before animal or human studies, supporting discovery and IND planning and reducing or replacing animal testing. The example shown illustrates predicted drug vs. free target in plasma and tissue concentration profiles (vascular, interstitial, endosomal, total), demonstrating how PBPK links in vitro measurements to clinical exposure and effect.

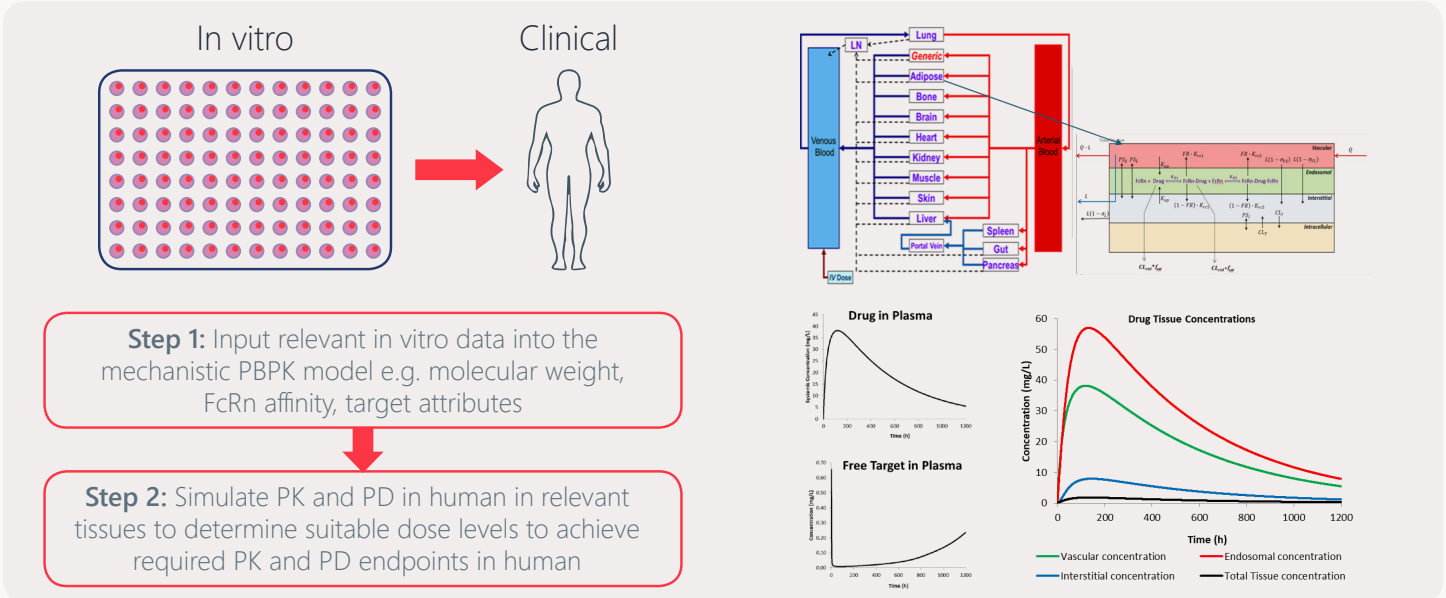

Figure 3. Predicting FIH PK with PBPK Modeling

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Likewise, QSP modeling platforms like the Certara IG Simulator can predict important issues like immunogenicity (IG) and the likelihood of anti-drug antibody (ADA) formation (Figure 4). Most mAbs and other biologic drugs can trigger the generation of ADAs. This immunogenic response can decrease drug efficacy since neutralizing ADAs can decrease drug exposure. An FDA survey of over 100 biotherapeutic products found that the incidence of immunogenicity was nearly 90%, with efficacy being impacted in almost half of the cases.

Animal models are generally poor predictors of immunogenicity. Therefore, Certara scientists developed the IG Simulator, an in silico biosimulation platform, in a consortium with major pharma companies. It has been calibrated and validated with dozens of clinical reference mAbs and proprietary compounds. The IG Simulator does not require animal data and uses AI and machine learning algorithms, combined with in vitro assay inputs, to simulate virtual trials before any clinical data is available.

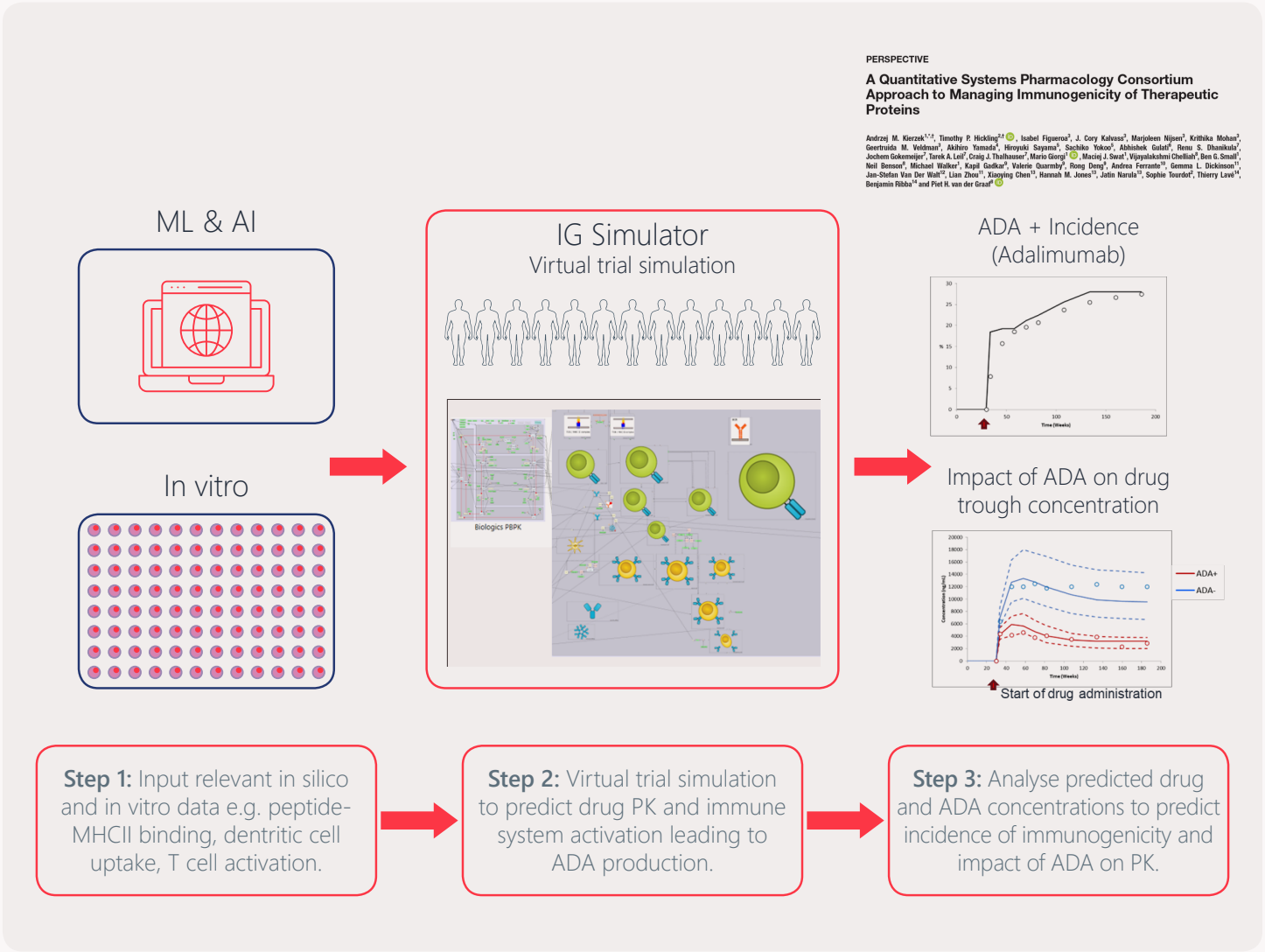

Figure 4. Predicting clinical immunogenicity and anti-drug antibody formation

Transitioning to non-animal studies: a practical roadmap

drug developers need confidence that NAMs will be accepted by regulators. Without clear guidance from the agency and consistent review practices, sponsors will default to performing animal testing, even when NAMs are more scientifically valid.

Pharma companies should engage with regulators early, build cross-functional teams, and leverage partnerships to implement non-animal approaches. Regulators now expect holistic submission packages (Figure 5). Sponsors should combine NAMs to develop their drug's evidence base. The NAMs they use must be reproducible, standardized, and benchmarked against clinical outcomes. To ensure both regulatory and patient trust, NAMs must confer predictive power that meets or exceeds traditional animal tests.

Theme	Old Model (Animal-Centric)	New Model (NAM-Centric)
Default Testing	2-species animal studies	Human-based NAMs first
Validation Standard	Concordance with animal data	Prediction of human outcomes
Regulatory Mindset	Historical precedent	Managed innovation
Evidence Structure	Single study endpoints	Integrated multimodal evidence
Global Coordination	Fragmented	Proactive harmonization

Figure 5. Integrated Evidence Philosophy - Scientific Rigor Remains Paramount

Transitioning from animal-based testing to NAMs requires a "weight of evidence" approach (Figure 6). Instead of directly replacing each animal test, sponsors should weigh multiple factors, including the disease being treated, clinical need, and drug target information, as well as clinical, modeling, and in vitro data. Together, these data streams form a more complete and human-relevant picture of drug safety and efficacy.

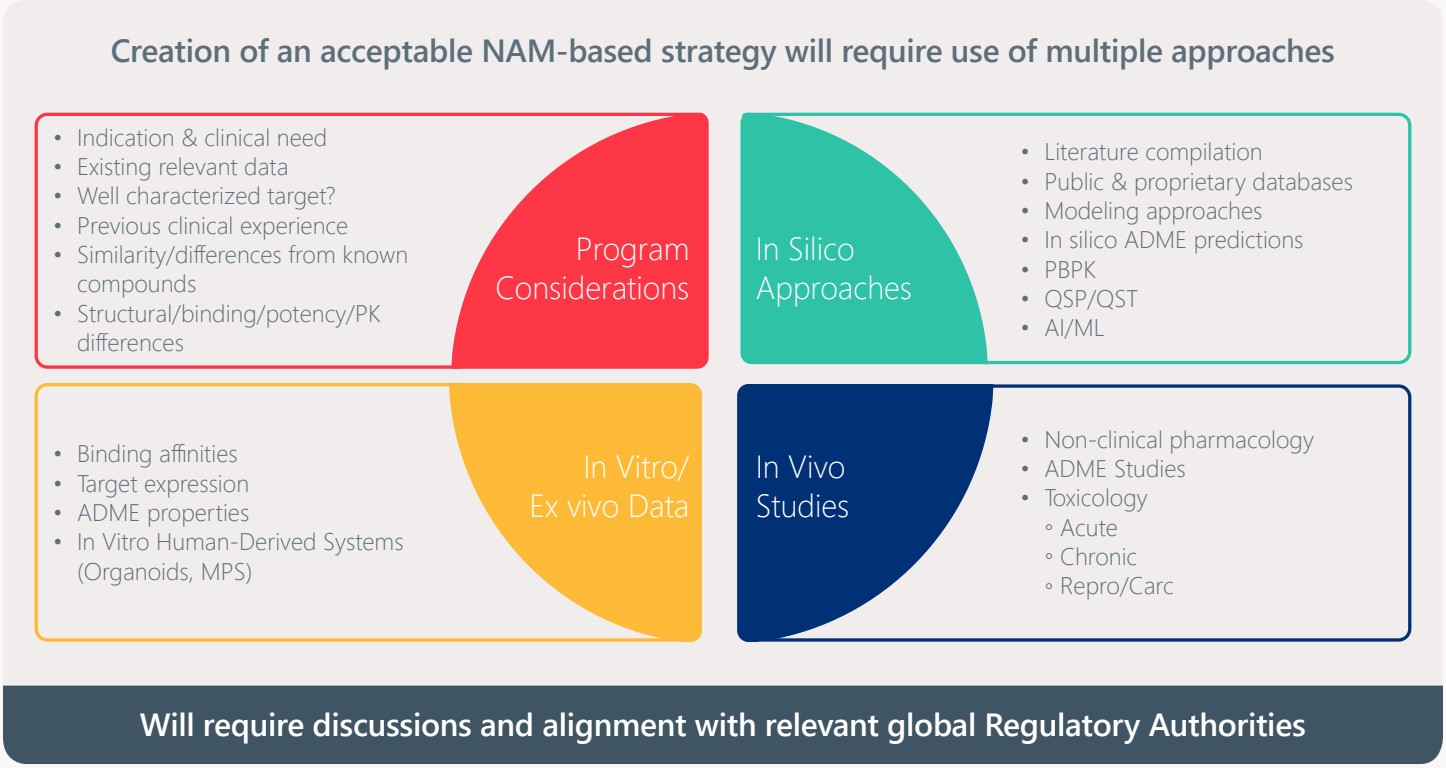

Figure 6. Moving to a "Weight of Evidence" Philosophy

Certara's Non-Animal Navigator™: Guidance tools for integrating NAMs into pre-clinical pipelines

Certara's Non-Animal Navigator solution helps companies adapt by selecting and optimizing their NAM strategies (Figure 7). We do this by first conducting a gap analysis of their current program. Based on this assessment, we then tailor a bespoke software and services solution for the particular asset. Using this approach helps our clients accelerate development, manage costs, and ensure regulatory alignment.

This solution can support each stage of monoclonal antibody (mAb) development:

- **Early Discovery:** Systems biology, PBPK, and bioinformatics guide target validation and early compound optimization.
- **Lead Optimization:** Traditionally relies on animal models for in vivo PK/PD and toxicology studies, but biosimulation enables integration of computational and experimental insights.
- **First-in-Human clinical studies:** Model-based projections inform starting dose, dose escalation scheme, and efficacious dose predictions.

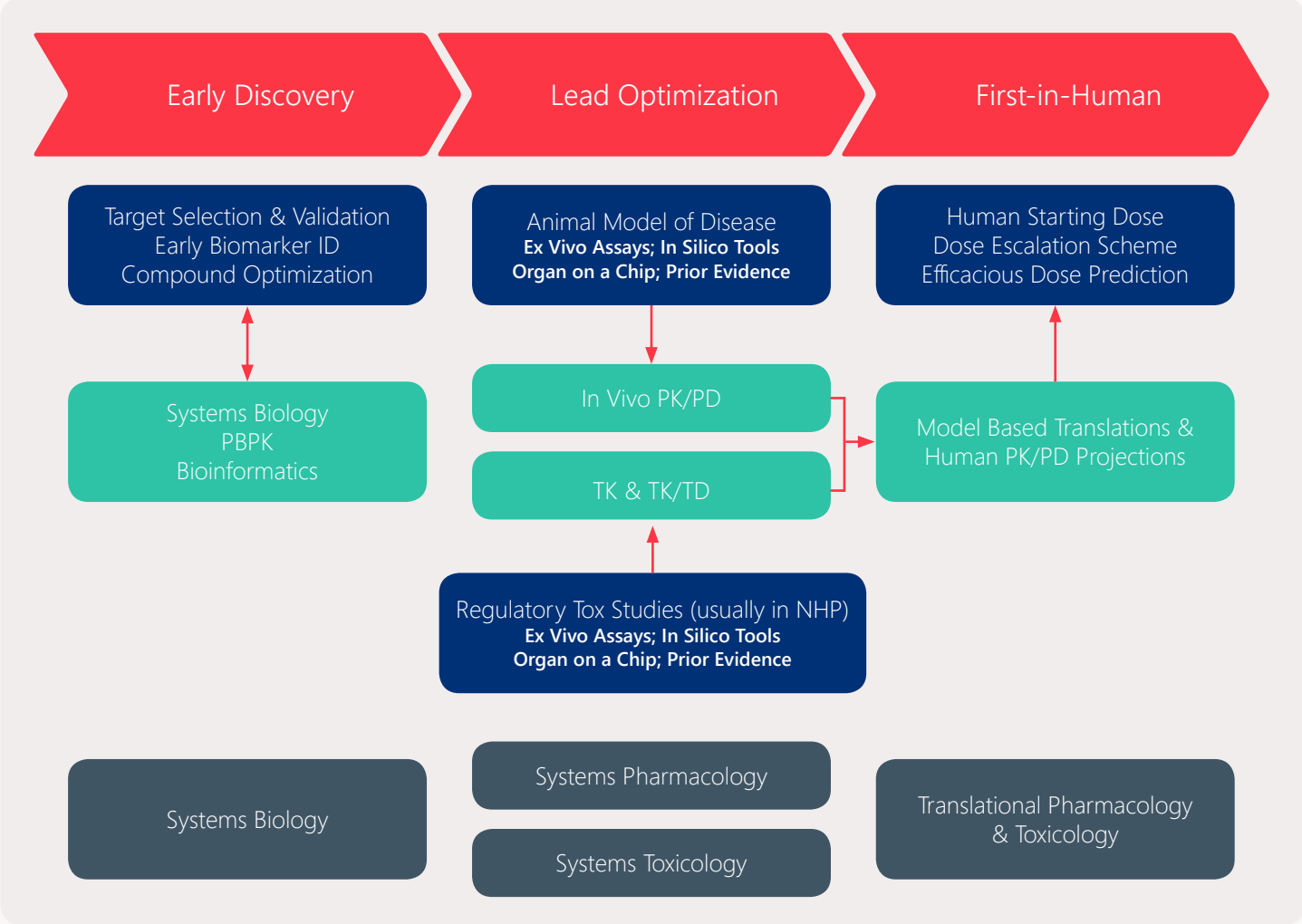

Figure 7. Biosimulation Framework for Pre-Clinical Monoclonal Antibody Development

Looking Ahead

The pharmaceutical industry's transition to non-animal testing is inevitable. Human-relevant, data-driven science powered by AI and biosimulation will shape the future of ethical drug development. Learn more by watching this webinar: **https://www.certara.com/on-demand-webinar/are-you-prepared-for-the-fdas-phase-out-of-animal-tests-for-mabs/**

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About Certara

Certara accelerates medicines using biosimulation software, technology, and services to transform traditional drug discovery and development. Its clients include more than 2,400 biopharmaceutical companies, academic institutions, and regulatory agencies across 70 countries. Learn more at certara.com.

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