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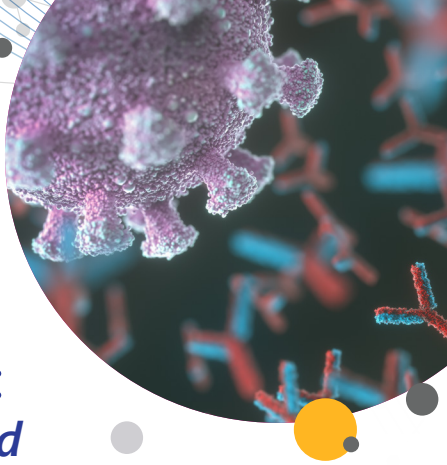


How Modeling & Simulation is Addressing the Immunogenicity Challenge:

An academic nicety is now a drug development and regulatory differentiator

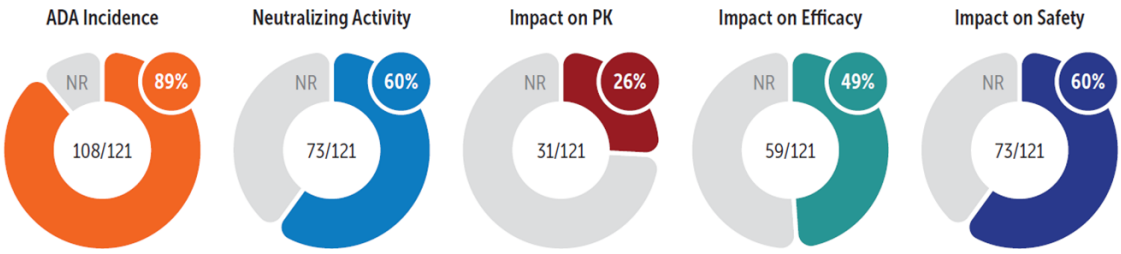
By Piet van der Graaf and Andrzej Kierzek

How big is the Immunogenicity Challenge?

In 2022, the US FDA released draft guidance on Immunogenicity (IG) Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling. The agency defines IG as the ability of a substance to trigger an immune response in the body. The guidance focuses on undesired IG, or the propensity of the therapeutic protein product or other applicable drug product to generate an immune response to itself, a related structure, or product complex: and to induce immunologically-related adverse events. This guidance recommends the use of a new dedicated IG subsection in the CLINICAL PHARMACOLOGY label section that will summarize IG data in one location in the label.

In short, unwanted IG is a significant challenge. An evaluation of the FDA's clinical pharmacology review of biological products approved prior to February 2015 revealed that 89% of all investigated biologics reported the incidence of anti-drug antibodies (ADAs), 60% reported immunogenicity impact on safety, and 49% indicated an impact on efficacy. Furthermore, of the 121 approved biological products, 26% (n = 31) reported that immunogenicity affected pharmacokinetics (PK).[1] A second reference states that drug IG manifests in the generation of ADAs, with some monoclonal antibodies showing IG of up to 70% in patients.[2]

Reporting Status of Immunogenicity Data Components (Reported vs. Not Reported)



NR: Not reported; ADA: Binding, anti-drug antibodies: PK: Pharmacokinetics

Source: *AAPS J.* 2016; 18(2), 395–403.

Supporting the rationale for the new guidance, which creates a new label section dedicated to IG, FDA recently held a forum that identified the range of immunologically related adverse clinical events[3]:

- ADA Impact on Pharmacokinetics, Pharmacodynamics, Efficacy
  - *Can result in a change in efficacy*
  - *Can alter pharmacokinetics (e.g., bioavailability)*
  - *Can alter pharmacodynamics*

- Safety: potential immune responses
  - *Cross-react with native protein or receptor*
  - *Potentiate biological product*
  - *Immune complex formation*
  - *Hypersensitivity reactions*
  - *Cytokine release syndrome*

A clear takeaway from the FDA workshop is the recommendation for including pre-clinical in silico IG risk assessment for novel modalities

The bottom line is that IG can have a significant impact on the exposure and effects of the drug, necessitating a quantitative analysis of IG risk factors.

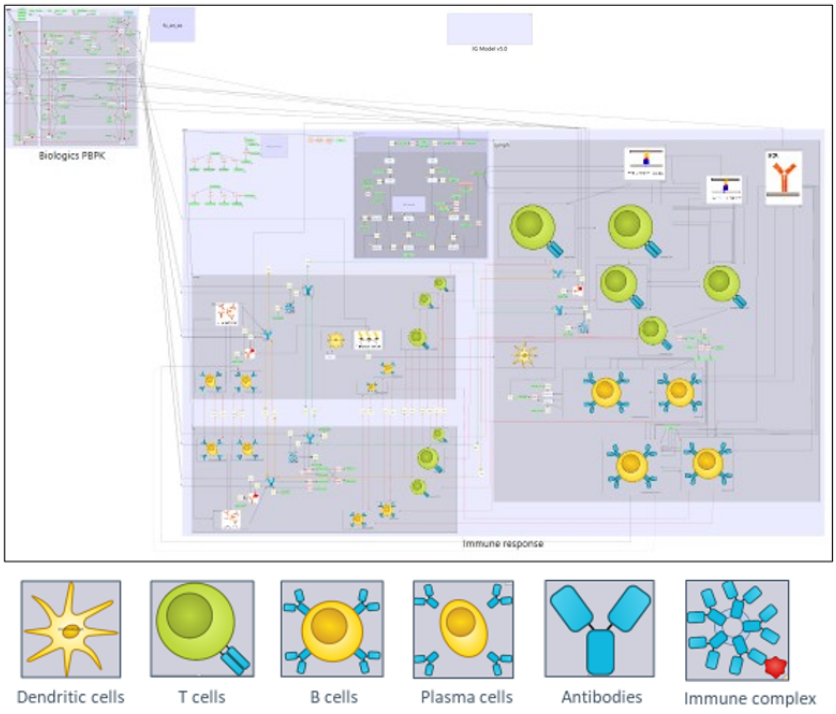
Model-informed Drug Development Approaches to Managing IG

Contributing to the new guidance was a 2021 US FDA public workshop dedicated to Model-Informed Drug Development (MIDD) approaches for immunogenicity evaluation of medical products.[4] The workshop, with more than 2,000 registrants, was attended by experts in academia, industry, and regulatory agencies.

The opening session, "methodological advances in IG assessment," focused on the rapid advances of Quantitative Systems Pharmacology (QSP) for assessing, predicting, and managing IG for different diseases and contexts. Speakers from Johns Hopkins, Pfizer, BMS and Certara, all pioneers in the field, organized and led this program to address *in silico, in vitro* and *in vivo* assessments and how to best apply "learn and confirm" mechanistic modeling for human IG.

In 2017, a group of companies aligned with Certara, formed a consortium to develop a predictive tool to simulate clinical consequences of IG in drug development. Pfizer spoke about the original model used to create the IG Simulator, BMS spoke of its first application in drug development, and Certara shared the IG Simulator platform, as shown below:

Biological scope of IG Model V5

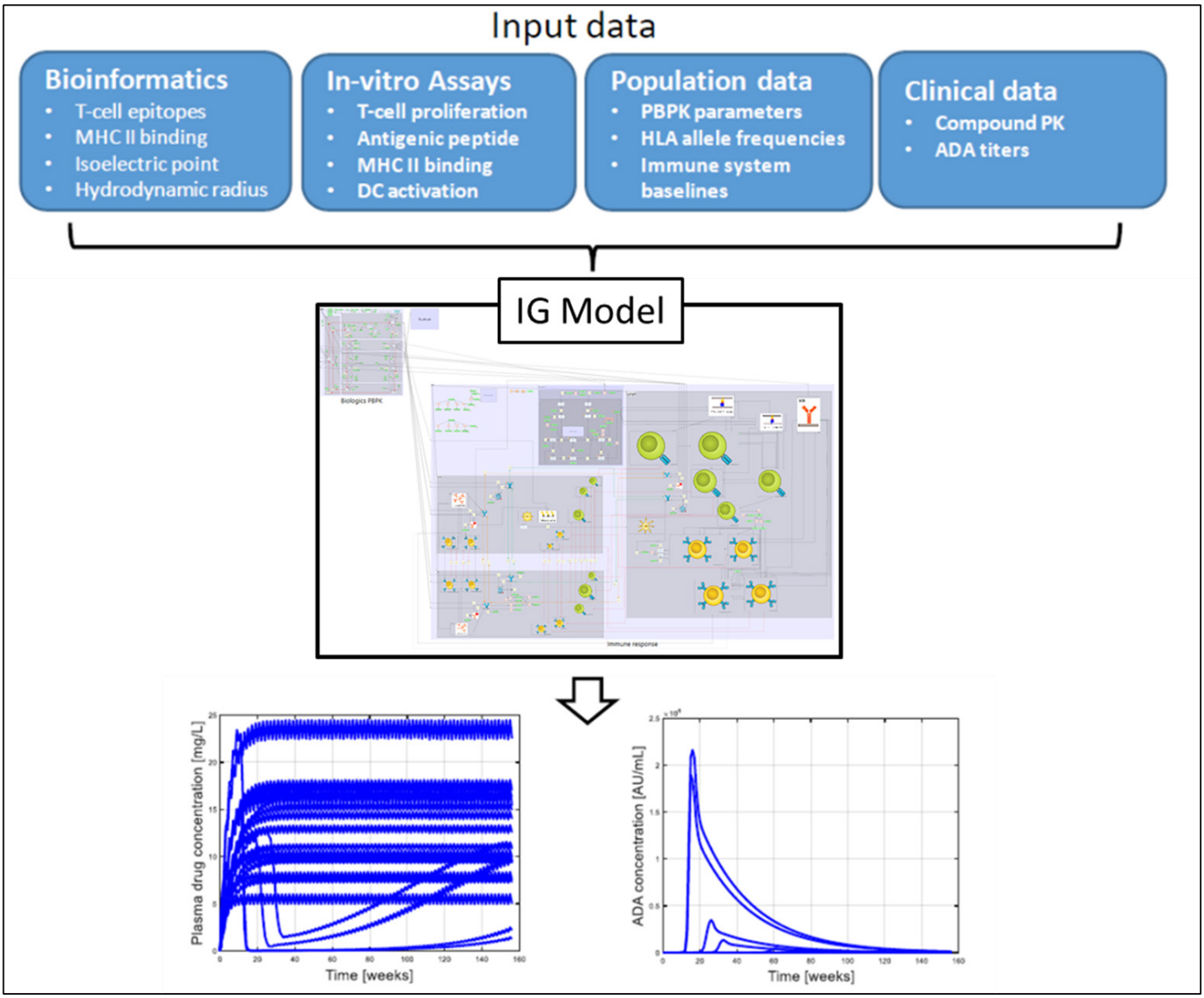


Variables	Lymph compartment	Vascular compartment	Plasma compartment
T cells	Naïve	Naïve	Naïve
	Activatedfrom naïve	X	X
	Memory	Memory	Memory
	Activatedfrom memory	X	X
	Functional	Functional	Functional
B cells	Naive	Naive	Naive
	Activated from naive	X	X
	Memory	Memory	Memory
	Activated from memory	X	X
DC cells	Matured	X	X
	Immature	Immature	X
ADA	IgG	IgG	IgG
	IgM	IgM	IgM
IC	IgG-Ag	IgG-Ag	IgG-Ag
	IgM-Ag	IgM-Ag	IgM-Ag
Plasma cells	X	Long-lived	Long-lived
	Short-lived	X	X

Main modules ofIG simulator

- Minimal PBPK model
- Bioinformatics input
- Antigen presentation module (MHCII)
- Cells circulation acrosscompartments
- Antibodies circulation across compartments
- Antibody affinity maturation

- The IG Simulator is a mechanistic, QSP platform to predict IG incidence and its impact on pharmacokinetics and pharmacodynamics.
- The IG Simulator predicts not only the propensity of the compound to induce immune response, but also the full-time profile of PK and ADA concentration.
  - *This is important, because the interaction of the drug with immune system is a dynamic process, and ADAs may have different impact on the drug at different doses and different timepoints.*
- The Simulator integrates various IG risk factors, quantitatively addressing the magnitude of immune response and impact, and simulating clinically relevant endpoints to inform drug development decisions.
  - *The tool can incorporate in silico/in vitro assessments (in silico prediction of epitope, MHC binding affinity of T-epitope, T cell stimulation potential) with in vivo assessments (response in animal model, Ab concentration and affinity) into a QSP model to predict IG.*
- The IG Simulator has been validated with > 20 clinical case studies, including mono and combination therapies.
- Using the Simulator, virtual patients are created and virtual trials conducted and analyzed in the same way as clinical data or biomarkers.



The IG Simulator at Work – Learn-confirm assessment from Roche

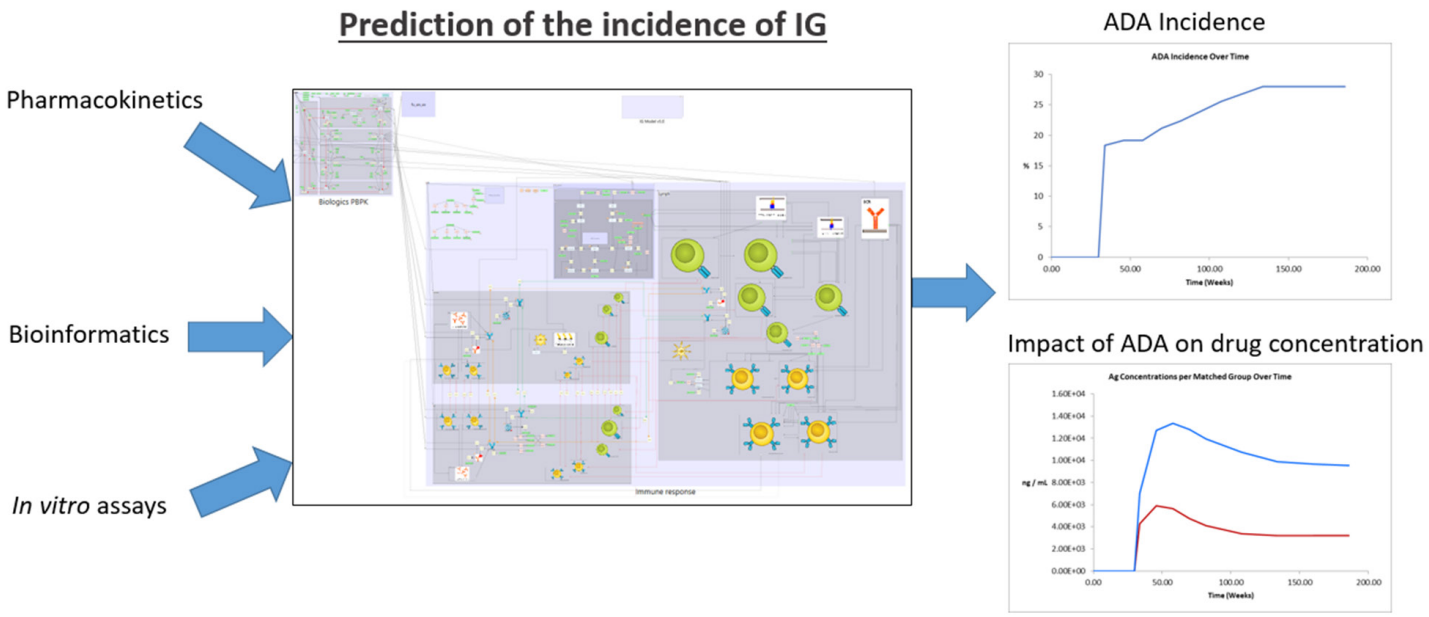
Roche, a member of Certara's IG Simulator Consortium, undertook a project to assess the credibility of the IG Simulator QSP model for three contexts of use in the drug development process through an unbiased evaluation[5], leveraging preclinical and clinical data to:

- Provide an unbiased IG Simulator assessment by blinding the modeling operator to experimental outcomes,
- Extend the evaluation of the IG Simulator both in terms of the number of compounds assessed and by using a realistic drug development setting,
- Explore how and whether additional data from preclinical in vitro assays can be used to improve predictions,
- Adjust the platform's workflow to allow its application to real-world clinical study designs.

The project was performed in a stepwise manner, based on ten monoclonal antibodies (mono- and bi-specifics), four of which are considered immuno-stimulating. Data are organized in eleven datasets with three from Phase I single-ascending dose trials, seven from combined Phase I/II multiple dose trials, and one from a multiple dose Phase III trial. The number of subjects per dataset ranges from 12 to 182. Analyses were conducted in the three key phases—discovery, preclinical, and clinical.

Per the study: "The MIDD platform developer considers this evaluation of a large set of real-world case studies a unique example of a development of a rigorous QSP platform through a sustained, collaborative "learn-and-confirm" approach. Invaluable insights into the model framework, integration of *in vitro* data, and the associated workflows were gained. The lessons learned will be incorporated into the next version of the IG Simulator model and software. They highlight that the lack of experimental data on absolute ADA concentrations is a major impediment in the field, which emphasizes the critical importance of the parallel evolution of sophisticated QSP platforms and matching experimental and clinical approaches. They further identified opportunities in developing meaningful methods for the quantification of exposure loss, and the IG QSP Consortium is currently working on this."

The sponsor highlights the unmet need for IG prediction during drug development through qualified MIDD platforms. Therefore, they look forward to advances in performance and credibility of the IG Simulator triggered by this and future performance assessments.



Next Steps

Amazing progress has been made in using QSP and other MIDD approaches in novel drug development, spurred most recently by the need to address COVID-19 and to inform and predict dosing for newer therapeutic approaches such as gene therapy. The Roche study is but one example of how IG risk assessment can be performed quickly to answer pressing questions and guide clinical study design. A clear takeaway from the FDA workshop is the recommendation for including pre-clinical *in silico* IG risk assessment for novel modalities. Widely used in biologics development, the Simulator can support lead candidate selection/optimization, translational science, determine IG risk, and predict impact on untested and special populations such as pediatrics by creating and simulating virtual patients. While under a program of continuous development, refinement and validation, the Certara IG Simulator is being used for the aforementioned predictions in discovery, preclinical and clinical settings. Finally, the US FDA has obtained a license of the Simulator.

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About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions, and regulatory agencies across 62 countries.

For more information visit www.certara.com or email sales@certara.com.

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