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Immunogenicity Prediction and Dose Optimization using Clinically-Validated *In Silico* Modeling & Simulation

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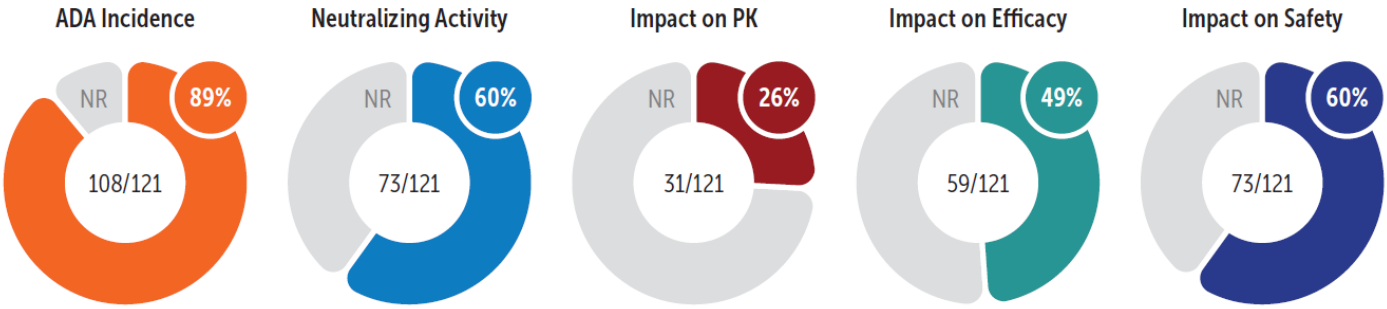
IMMUNOGENICITY PREDICTION AND DOSE OPTIMIZATION USING CLINICALLY-VALIDATED IN SILICO MODELING & SIMULATION

As defined by the US FDA, Immunogenicity (IG) is the ability of a therapeutic product to trigger an immune response in the body. That response can be desired IG to support vaccine and allergen response or undesired IG causing immunologically related adverse events. Figure 1 provides a summary of the types of impact from undesired IG. This white paper focuses on how modeling and simulation (also called model-informed drug development or MIDD) and specifically, a quantitative systems pharmacology (QSP)-based approach can be used to predict and better manage undesired IG (and in the case of vaccines, desired IG) and as a tool to guide clinical and regulatory decision-making in drug development.

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.

Figure 1.

Impact of IG on critical drug development parameters of safety and efficacy

The Rationale for QSP

QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. QSP can provide insight early in the development process (for example, predicting IG from protein sequence alone or extrapolating from pre-clinical assays) and ultimately be used to leverage vast amounts of biological and pharmacological data to address larger challenges such as phase 2 failures. In short, QSP enables the understanding of disease pathophysiology to identify and test therapeutic strategies in virtual trials with virtual patients.

QSP links principles and best practices from pharmacokinetic-pharmacodynamic (PK/PD) modeling on the one hand and systems biology on the other. It is the pharmacological discipline that through mathematical modeling tries to build confidence in and understanding of the therapeutic ligand and its biological target in the context of a specific disease.

As shown in figure 2, the main output from QSP models are virtual patients and virtual trials which are simulations of actual clinical trials. One obvious advantage of this *in silico* approach is that we are not constrained to using data that have already been obtained in actual patients, but we can simulate a trial that has not yet been performed, for example to guide first-in-human (FIH) dosing from preclinical data. A virtual patient can be a replicate of an actual specific individual and mimic characteristics such as body morphology, age, disease state, co-medication etc. From there, we can run many virtual trials exploring different clinical study designs, dosing regimens and combination therapies in different patient populations. Ultimately, we can create a Virtual Twin™ of a given patient delivering on the promise of precision dosing.

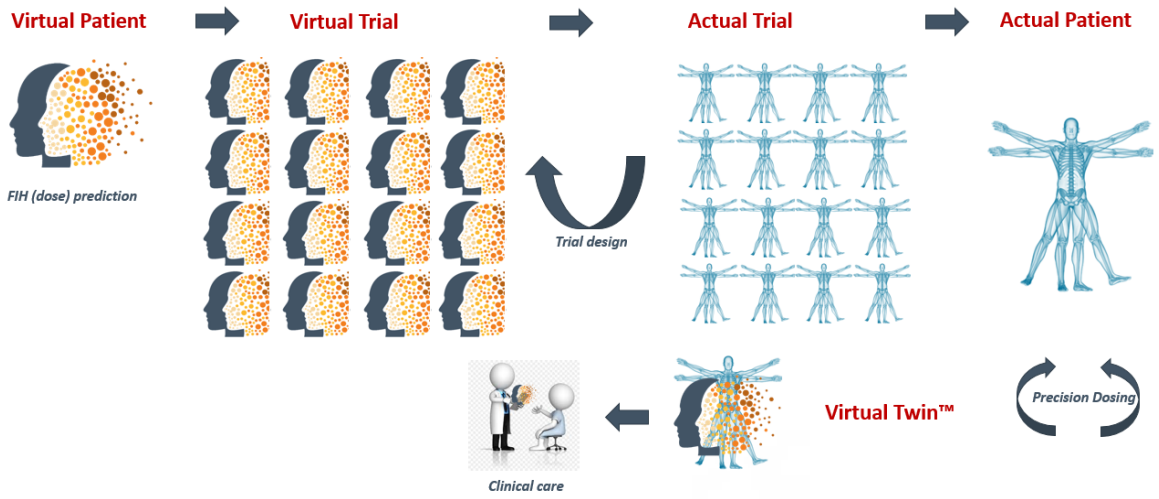


Figure 2.

QSP creates virtual patients that are then replicated and expanded to conduct virtual trials which inform and enable reverse translation from actual clinical trials

QSP, IG and the Regulatory Perspective

The FDA has been promoting MIDD since 2004 with the inception of the Critical Path Initiative (https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative). Under its most recent Prescription Drug User Fee Act (PDUFA) VI, and to further advance the technology, the agency launched a MIDD pilot program and included focused education on four key topics. On June 9, 2021, the agency convened a full-day workshop on one of those topics, IG, drawing more than 2,000 registrants. Certara supported that workshop via scientific presentations (both alone and with several leading pharma partners), panel discussions and as Key Opinion Leaders. The workshop recording, which included sessions on anti-drug antibodies (ADA), vaccines and new modalities such as gene and cell therapy is available at https://www.youtube.com/watch?v=7mS-jY4RGls.

Per FDA, "There is an increasing number of examples of QSP's role in guiding drug development. It can be credibly argued that the real impact of QSP is to de-risk a drug development program as it progresses. It is not surprising, then, that most case examples

of QSP center around key drug development considerations, such as hypothesis generation, compound selection/prioritization, translational biomarker development, and nonclinical and clinical trial design (https://pubmed.ncbi.nlm.nih.gov/30924594/). QSP played a lead role at the June 9 FDA workshop, and in the same week Certara presented the scientific and application progress of the IG Simulator to EMA in an Innovation Task Force briefing meeting. Similar invitations to discuss the IG Simulator have been received from other regulatory agencies, including PDMA and MHRA."

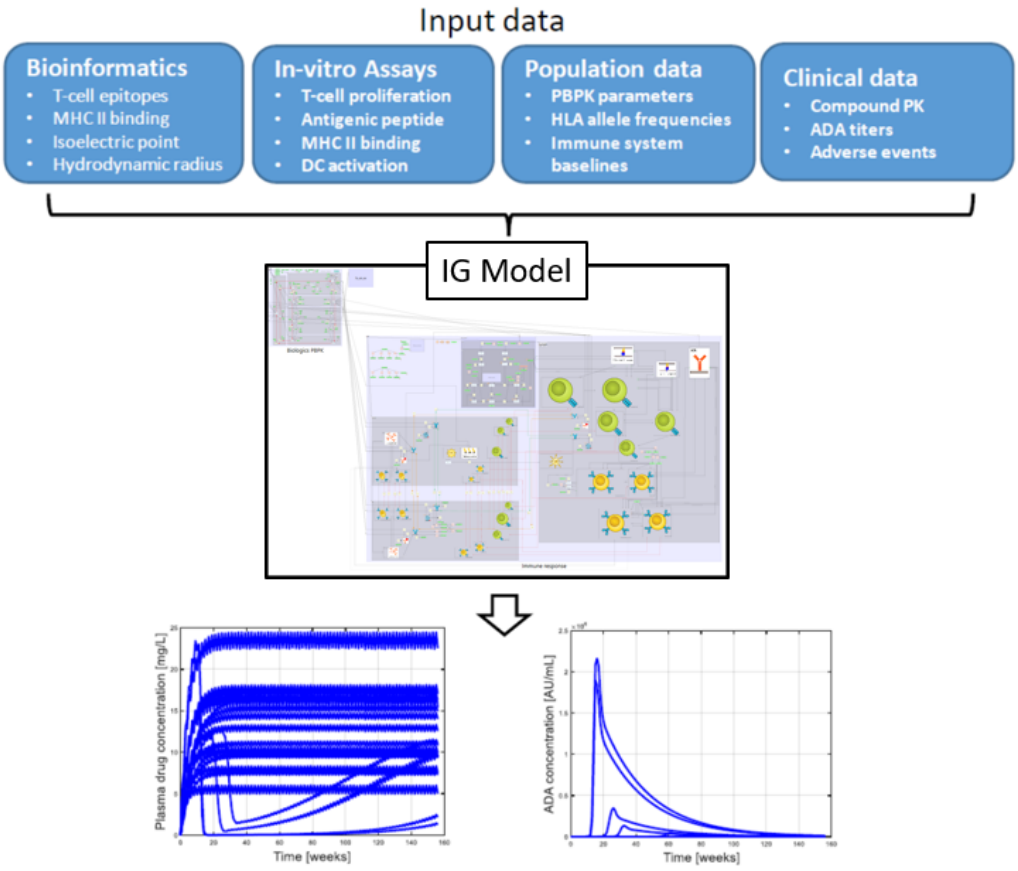
The Immunogenicity Simulator

In 2017, Certara established a consortium with seven major pharma companies to develop the IG Simulator which is a QSP platform to predict and manage immunogenicity of biologic therapeutics in drug development and patient care. The consortium is now in its fifth year and version four of the Simulator has now been validated with some 20 clinical case studies.

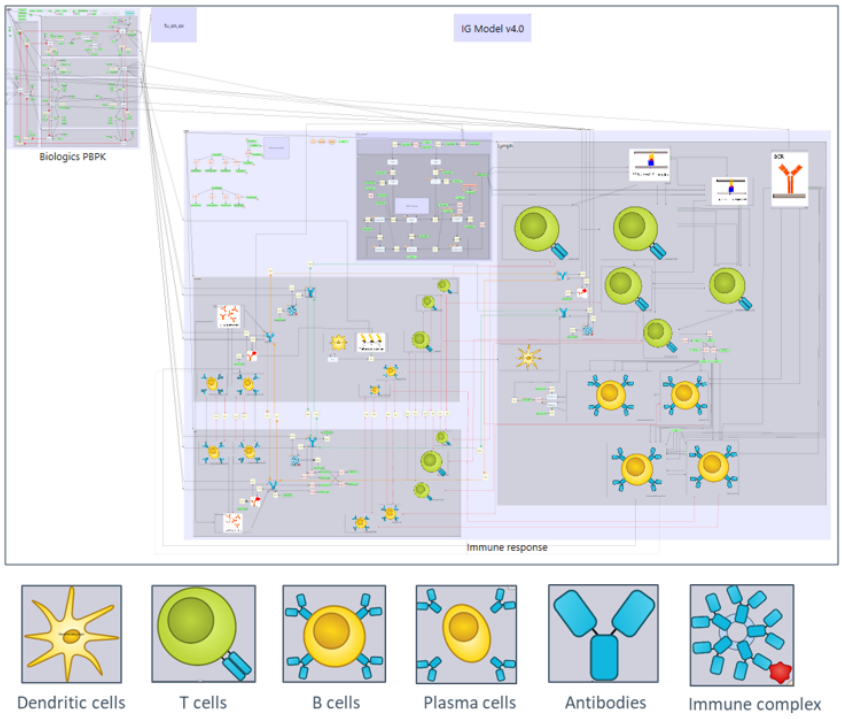
Importantly, unlike other tools, the IG Simulator (figure 3) does not *only* predict anti-drug-antibody (ADA) incidence but, uniquely, also the impact on pharmacokinetics (PK) and hence also pharmacodynamics (PD). It can integrate a variety of different input data ranging from protein sequence, *in vitro* and *ex vivo* assays, population and demographic parameters and actual clinical data.

Figure 3.

Certara's IG Simulator integrates predicted and experimental inputs to generate virtual patient simulations creating virtual trials from real and simulated subjects



A summary of the biological scope of the model and biological process map as seen by the user in our software (figure 4). The model contains naïve, memory and effector T-cells and B-cells in relevant physiological compartments. We model antigen presentation and dendritic cells. The model explicitly accounts for IgM and IgG anti-drug antibodies and formation of immune complexes. We model cell circulation, antibody and compound distribution between compartments. We have detailed model of antigen presentation accounting for HLA genotype and the model of antibody affinity maturation.



Variables	Lymph compartment	Vascular compartment	Plasma compartment
T cells	Naïve	Naïve	Naïve
	Activated from naïve	X	X
	Memory	Memory	Memory
	Activated from memory	X	X
	Functional	Functional	Functional
B cells	Naïve	Naïve	Naïve
	Activated from naïve	X	X
	Memory	Memory	Memory
	Activated from memory	X	X
DC cells	Matured	X	X
	Immature	Immature	Immature
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	X
	X	Short-lived	X
Main modules of IG simulator			

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

Figure 4.

The IG Simulator contains the key cellular players of human immune response all embedded in the major compartments, plasma, vascular space and lymph

The IG Simulator has an important role to play in the development of biotherapeutics and can guide decision making at every stage of the R&D cycle. The simulator predicts the impact of IG on PK and an initial risk assessment can be made based on sequence only in the absence of any further data. By following the MIDD “learn-and-confirm” principle, the model can be continuously updated and refined for a specific product throughout its life cycle from preclinical research to late-stage development. Due to the mechanistic nature of the model and the fact that it is coupled to a physiologically based pharmacokinetics (PBPK) platform, it can be used for extrapolation to specific and special populations as well as assessment of the impact of covariates, co-medication, dosing regimen and route of administration.

Case Study – IG Risk Assessment – Extrapolation from Pre-Clinical to Clinical

The IG Simulator can support drug development as a compound's companion model extrapolating from pre-clinical to clinical data as shown in figure 5. It can predict ADA and the impact on PK based on the compound sequence information alone. As the clinical program progresses, we add parameters inferred from *ex-vivo* data to improve quantitative accuracy which can then be used to make predictions for the next stage of the program.

The Simulator can used to inform choices between compounds for which *ex-vivo* assays have been conducted and inform the design of FIH trials. The model informed with FIH data can then be used to design larger trials, dosing regimens and intervals to minimize the impact of IG. In later stages of drug development, the validated model can be applied to extrapolate to special populations such as groups with specific HLA genetics, age and disease groups. Finally, the model instantiated with individual patient data can enable the creation of virtual twin simulations to achieve precision dosing.

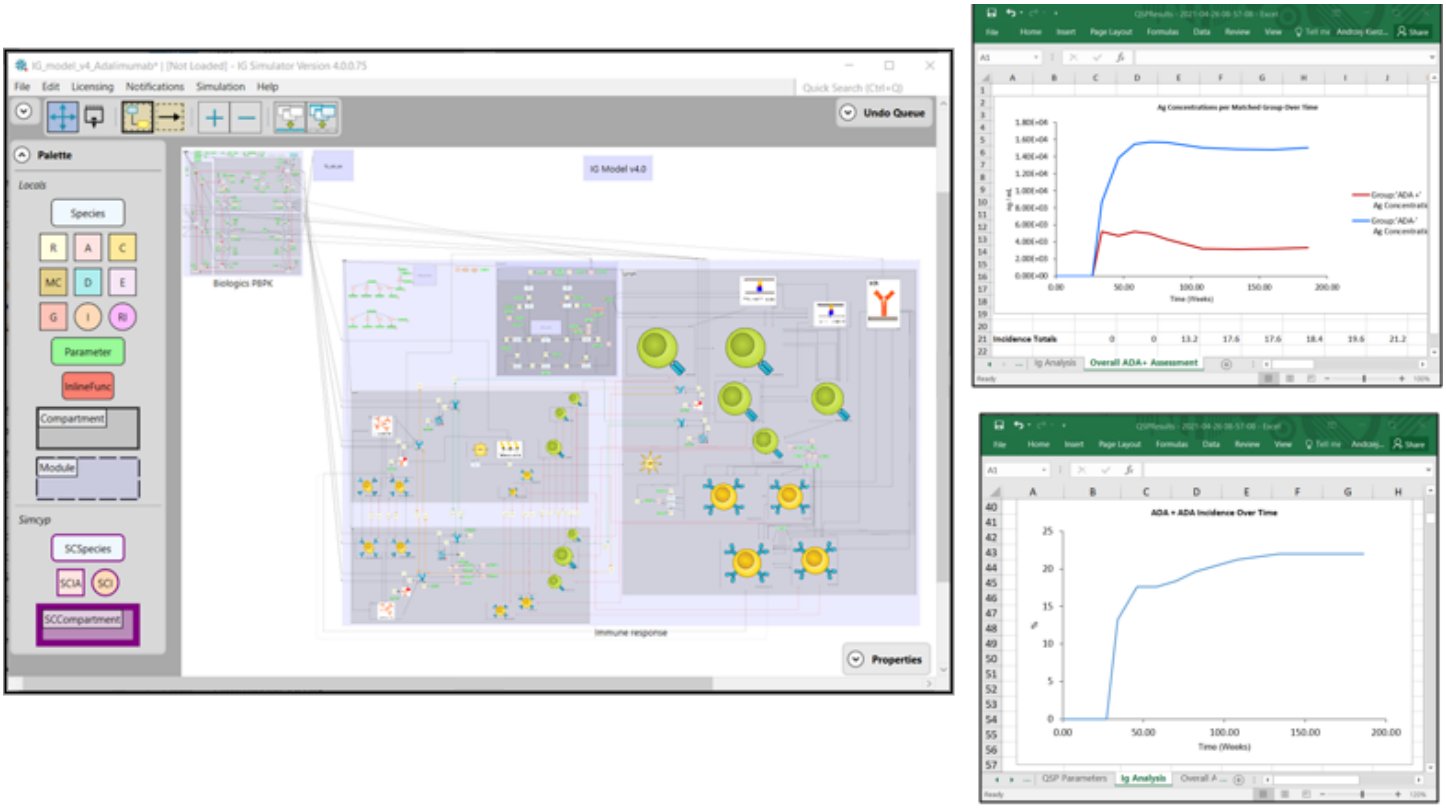


Figure 5.

The IG Simulator serves as a "dynamic document" with the simulations accompanying the entire compound development from pre-clinical onward

Case Study – Vaccines

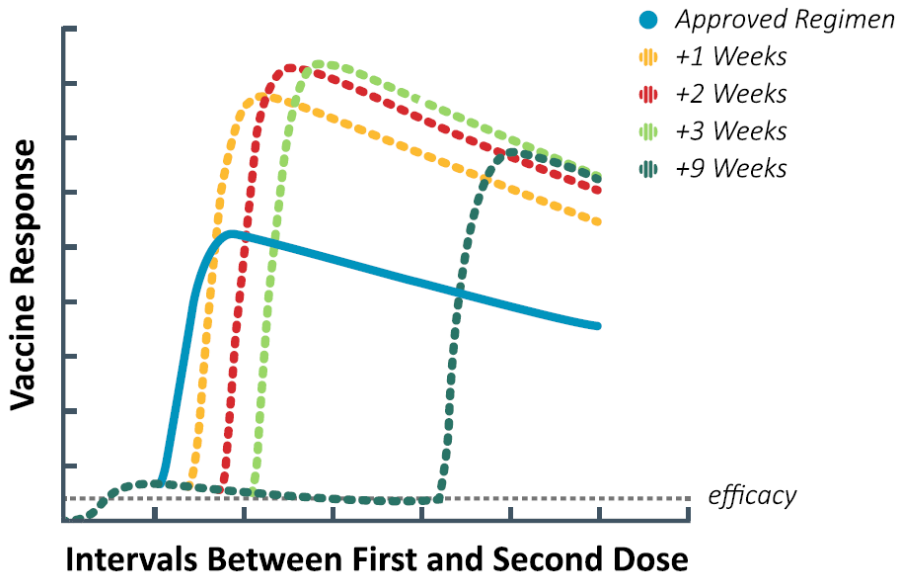
When the pandemic hit, we realized that our IG platform could be repurposed, calibrated and validated for COVID-19. Instead of trying to minimize the immune response as was the goal for the original IG model, the team switched its focus to maximizing the immune response for the COVID-19 vaccine. To be effective, a vaccine needs to induce an immune response and create an immune memory in the body. Then, the next time the virus, which looks very much like the vaccine protein, enters the body, the body will recognize it and respond very quickly.

After evaluating the model with early literature data, we ran a small pilot where we put the spike protein sequence into our Simulator which predicted a meaningful antibody response. Leveraging the Simcyp PBPK Simulator, Certara's model generates virtual populations of different ages allowing a series of virtual clinical trials to be run using the COVID-19 vaccine model to determine which vaccine dose will generate the maximum antibody response for each age group. The model also allowed the team to predict immunological responses that may not be measurable in actual patients such as the level of memory B cells which is used to compare and optimize various dosing schedules in the virtual trials.

We began working with a major pharma company and helped them design a clinical trial for a novel mRNA Covid-19 vaccine that hadn't been tested in humans using our platform, and these results were submitted to and accepted by regulators in support of a Phase I

Figure 6.

Certara's Vaccine Simulator determined the optimal timing of intervals, boosters, mixing of vaccines and maximizing efficacy against variants



trial. Moreover, on February 15th we submitted publication showing predicted dependence of antibody response on interval between two doses (https://arxiv.org/abs/2102.07610, https://pubmed.ncbi.nlm.nih.gov/34331834/).

Since that submission, the optimized dosing schedule of eight week intervals that we predicted with our simulator was determined to align with the optimal clinical results of 8 weeks (https://www.pitch-study.org/PITCH_Dosing_Interval_23072021.pdf, https://pubmed.ncbi.nlm.nih.gov/34301631/) as shown in figure 7. We note, that re-purposed IG Simulator correctly predicted conclusions of a clinical trial disclosed after simulation results were already published. Encouraged by this important validation, we are now applying IG Simulator to design of Phase II/III trial with our client.

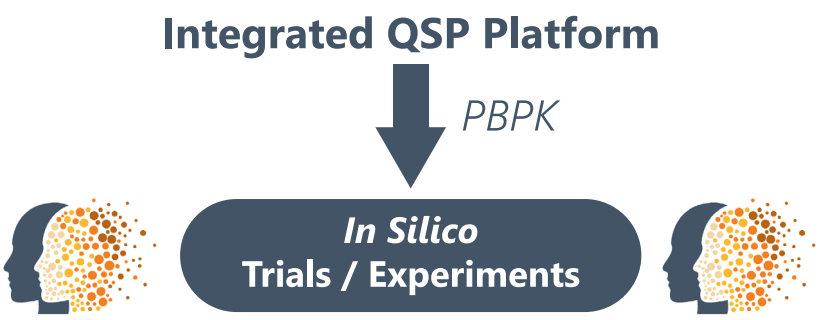
Summary and Ongoing Work

IG risk factors relate to structural properties (sequence), formulation, route of administration, patient characteristics, dose and regimen. The clinical consequences of IG can affect ADA incidence, change of PK and PD, and loss of efficacy. And while the impact of IG is still not well understood, it can be managed by using tools such as the Simulator for translational and clinical decision-making.

At Certara, we are investing in the development of platform models to guide decision-making across R&D, including IG, monoclonal antibodies, bi-specifics, and gene therapy (figure 7). The modular nature of these platform models allow for a continuous "learn-and-confirm" development and rapid expansion into new areas such as novel therapeutic gene therapy modalities and biosimilars. An example is the COVID-19 vaccine case study where the platform was developed in less than six month from conception to regulatory filing.

Figure 7.

Certara develops QSP platforms to address a range of modalities, diseases, and pathways that can be combined for bespoke programs



We believe that biosimulation and virtual patients can be used to address critical questions in IG and new modalities. This approach has a proven track record in expediting drug development and increasing the probability of success and is increasingly being adopted across the industry and by regulators.

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About Certara

Certara accelerates medicines using biosimulation software and technology to transform traditional drug discovery and development. Its clients include more than 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

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