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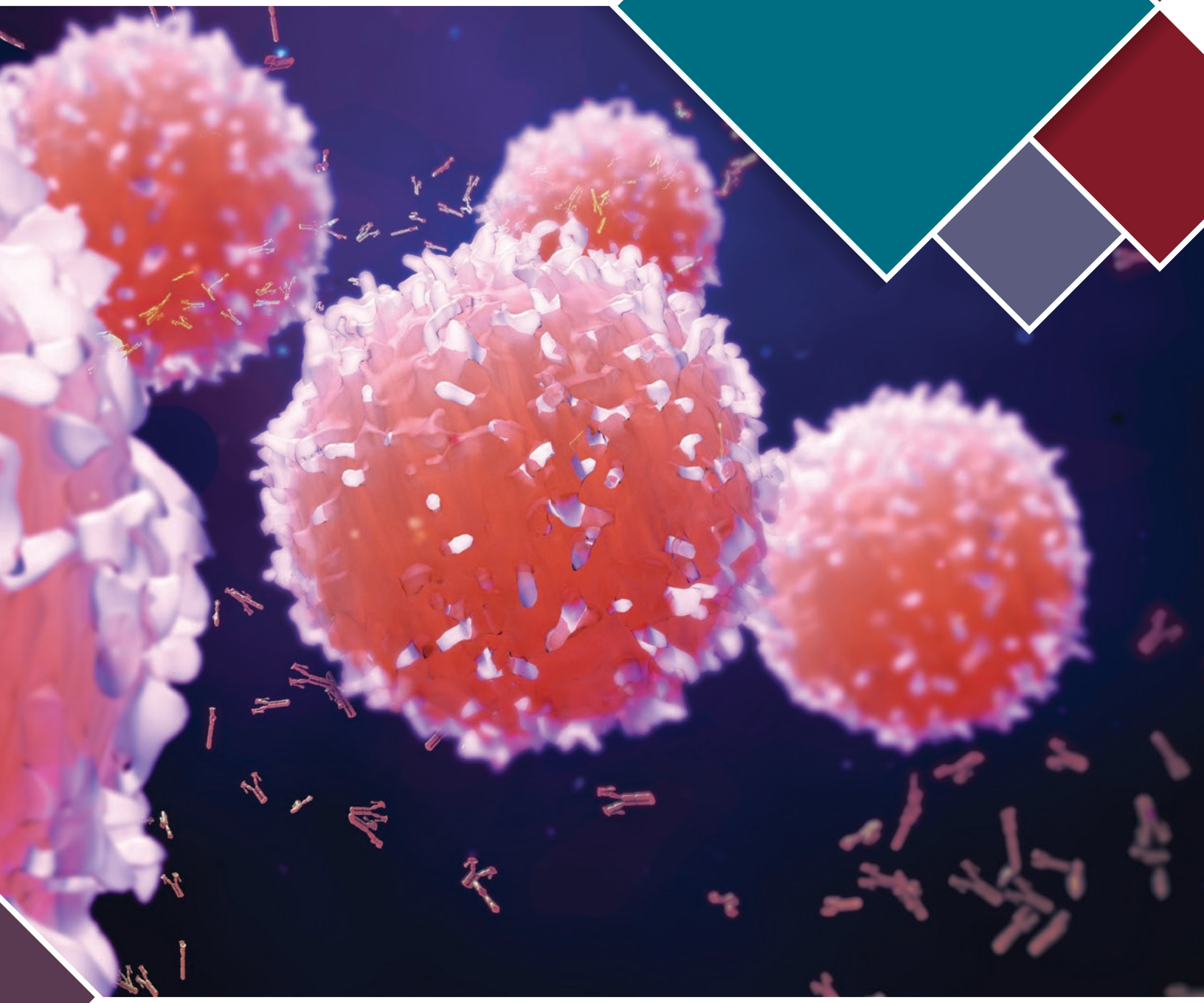


Managing Immunogenicity Using Quantitative Systems Pharmacology

Piet van der Graaf, Andrzej Kierzek, & Timothy Hickling

Managing Immunogenicity Using Quantitative Systems Pharmacology

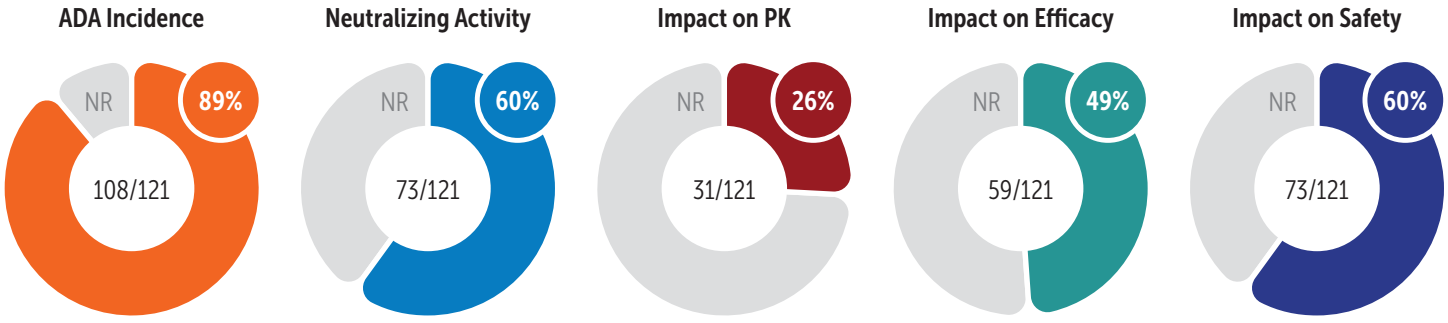
How Model-informed Drug Development Can Manage a Key Challenge in Biologics

Background

Biologic drug development is a rapidly evolving sector in the biopharmaceutical industry. Protein-based therapeutic drugs comprise monoclonal antibodies (MAbs), vaccines, recombinant hormones and proteins, antibody-drug conjugates, RNAi, antisense, blood factors, and other large molecules. As of 2017, biologics represent greater than 50% of drug candidates in development and represent an increasing percentage of new drug approvals.[1] Substantial advances in the fields of genomics, proteomics, metabolomics, bioinformatics, and other disciplines, combined with improved technologies and tools for biomedical analysis and diagnoses, have made a significant impact on biologic drug development. These innovations have led to a marked increase in approvals of protein-based therapeutics for oncological, rare autoimmune, and neurological diseases. Biologics offer high efficacy often with fewer side effects; the success of biologics, combined with an increasing vulnerable aging population, has led to a discernable rise in biologic drug development programs.

Although the success of biologics has been demonstrated, there are inherent operational and technological challenges associated with this complex class of drugs. One of these challenges—immunogenicity—has become a key area of regulatory interaction. Immunogenicity (IG) is defined by the FDA as the propensity of the therapeutic protein to generate immune responses to itself and to related proteins, or to induce immunologically-related adverse clinical events.[2] In a recent FDA review of 121 approved biological products, 89% of the products had reported immunogenicity, and in 49% of the cases IG impacted the drug's efficacy.[3]

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.

This white paper focuses on how a quantitative systems pharmacology (QSP) based approach can be used to predict and better manage immunogenicity, and as a tool to guide clinical and regulatory decision-making in biologics drug development. QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. In addition, highlights on the recent creation of the Certara QSP IG Consortium will be reviewed. The Certara QSP IG Consortium brings together leading biopharmaceutical companies in a pre-competitive environment to cooperatively develop an industry standard Immunogenicity Simulator that will predict IG of biologics and its impact on the drugs pharmacokinetics (PK), efficacy, and safety in diverse patient populations.

Managing IG has manifested as a challenge not just in development, but also in manufacturing and, in particular, patient care. QSP is now considered a valuable emerging technology that can help us better understand these challenges.

The Role of Model-Informed Drug Development in Modern Drug Development

Model-informed drug development (MIDD), also called modeling and simulation (M&S), has become essential to modern drug development, impacting all phases of the process, such as increasing our understanding of benefit/risk, determining go/no go decisions, assessing safety and efficacy of new therapies, guiding dose selection, developing safer, targeted, and more efficient trial designs, addressing the needs of special populations, identifying issues that need further characterization, evaluating alternative formulations and drug indications, and informing drug labeling decisions. Beyond the many ways that MIDD influences decisions and strengthens the science, it also enhances commercial value by reducing time and cost-to-market via smarter and potentially smaller or avoided studies. MIDD approaches such as PK and pharmacokinetic/pharmacodynamic (PK/PD) modeling, physiologically-based pharmacokinetic (PBPK) modeling, model-based meta-analysis (MBMA), and QSP have been embraced by regulatory agencies such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices (PMDA), and other agencies who have developed guidances for using quantitative *in silico* methods to support regulatory guidelines.

Dr. Scott Gottlieb, Commissioner of the FDA, has iterated the important role that MIDD plays in the 21st Century Cures Act, the FDA's new guidance for the industry for drug-drug interactions, the FDA Reauthorization Act (FDARA), and the most recent Prescription Drug User Fee Act (PDUFA) and Generic Drug User Fee Act (GDUFA) documents. Most recently, FDA Commissioner Gottlieb, as part of the FDA's ongoing drug modernization effort to promote the adoption of innovative approaches to drug development, announced the introduction of a pilot program for participating drug and biologics companies who will be able to meet with agency staff to "discuss the use of novel complex innovative trial designs (CID) for their clinical development programs." These CID approaches include "modeling and simulations to assess trial operating characteristics, the use of biomarker enriched populations, complex adaptive designs, Bayesian models and other benefit-risk determinations, and other novel designs."[4] Beyond FDA, the EMA recently upgraded their M&S working group to a working party, reflecting the greater role it is expected to play in regulatory decision-making over the coming years.

Adoption of MIDD by the FDA

Source: R. Madabushi, Office of Clinical Pharmacology, US Food and Drug Administration. Guidelines and Good Practices for Advancing Model-informed Drug Development: Gaps and Opportunities. American Conference on Pharmacometrics, October 2017

1990-2000
Early Days

- IVIVC
- PK/PD
- PopPK
- Pharmacometrics Group

2000-2010
Rapid Growth

- PopPK, D/R, E/R
- Guidance
- CTS and Disease Models
- Early days of PBPK research and application
- Division of Pharmacometrics (DPM)

2010-2017
Approaching Mainstream

- Routine application of pharmacometrics and PBPK for DDIs
- Early application of semi-mechanistic and mechanistic modeling in review and research
- Opportunistic standardization
- Regulatory acceptance of drug development tools
- Organizational growth, assimilation, and prioritization

Beyond 2017
Accepted Standard

- Development of standards for data, analysis, and processes
- Pathways for regulatory engagement
- Integration of various M&S activities throughout drug development
- Management of information and knowledge—disease modeling, PBPK 2.0
- Incorporation of newer approaches and technologies—QSP, Bayesian, etc.
- Leveraging real world data

In particular, the application of PBPK modeling has played a prominent role in MIDD and is used by regulatory agencies and the pharmaceutical industry across the drug discovery and development continuum to inform key R&D decisions for first-in-human dosing, formulation design, dosing in special populations, optimizing clinical trial designs, assessing drug safety, clinical efficacy, and predicting the likelihood of drug-drug interactions (DDIs).[5] PBPK and QSP are both mechanistic modeling approaches, however, QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process.

Quantitative Systems Pharmacology—Bridging Pharmacokinetics and Systems Biology

The explosion of high quality "omics" information—genomics, proteomics, transcriptomics, metabolomics, and others—at the start of the 21st century fueled the development of systems biology. Systems biology models disease by applying a nonlinear, integrative, quantitative, and holistic approach that uses biology, computational modeling, engineering, bioinformatics, and other sciences to understand complex biological systems and how perturbing these systems can cause disease.[6] According to Andrzej Kierzek, head of Systems Modeling, Certara UK, academic groups working in Systems Biology area over last 20 years have been creating mechanistic models of molecular networks underpinning behavior of the living cell. These models have now matured to the application in MIDD.

QSP is a relatively new discipline with enormous potential to improve pharma R&D productivity and inform decision-making across the drug development process from early discovery to Phase 3. QSP provides an *in silico* framework for constructing mechanistic, mathematical models of drug action. QSP focuses on the area between PK/PD and systems biology; it translates PK or exposure into pharmacological effect and builds on gaining insights from pharmacometric, PK/PD, and PBPK approaches with systems biology models of biological and biochemical processes. QSP models can be used to design first-in-human clinical trials, inform the mechanisms of drug efficacy and safety, and confirm drug target binding and modulation.[7] Once how much drug is at the site of action is known, QSP can help answer the following questions: How will the drug modulate cellular signaling to exert a pharmacological effect? What pharmacological action will it have at that particular organ? Answering these questions will provide insight into the mechanisms of drug efficacy.

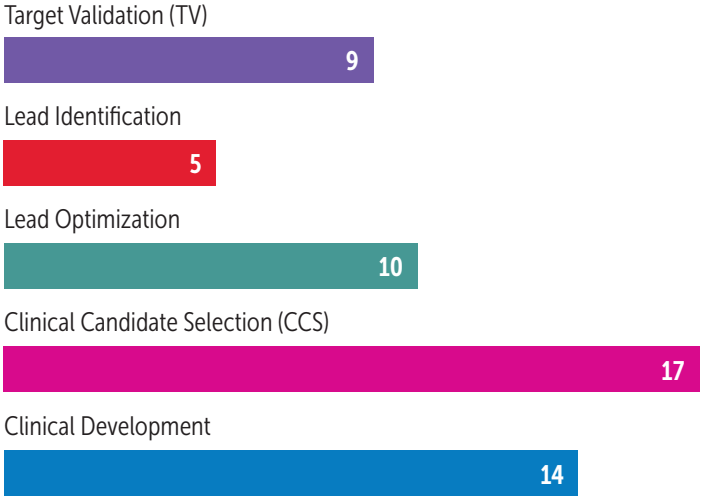
This approach can be used to predict how drugs modify cellular networks and how drugs impact and are impacted by human pathophysiology. QSP can also facilitate evaluating complex, heterogeneous diseases such as cancer, immunological, metabolic, and CNS diseases that commonly require combination therapies to control disease progression.[8] A key opportunity for QSP is to improve the drug attrition in Phase 2 clinical trials where about 80 percent of new drugs fail due to lack of efficacy. Many of the Phase 2 failures may be due to targeting the wrong mechanism or patient population or to suboptimal dosing. QSP can be used to augment current MIDD approaches to tackle failures years before the pivotal Phase 2 trial.

Being armed with this knowledge would enable sponsors to change their Phase 2 strategy regarding dose or dosing frequency, or drug combinations, well before the actual trials. Insights from QSP would also help them to influence the trial designs and rationally plan which patient subpopulation to target before running that make-or-break Phase 2 trial, making the difference between failure and success. In this respect, QSP is distinct from other MIDD approaches such as pharmacometrics since it helps to fill in the gaps between the early-stage PK understandings of PK and the late-stage understanding of drug efficacy using a mechanistic approach. QSP will help fill this void to address the problem of high attrition in Phase 2 trials, which will lead to a better understanding of efficacy and safety in clinical studies.

QSP also shows promise as an approach that can impact pre-clinical development. A recent cross-industry survey, conducted by the Drug Metabolism Leadership Group (DMLG) in the International Consortium (IQ) for Innovation and Quality in Pharmaceutical Development, assessed the landscape of using pre-clinical QSP modeling within the pharmaceutical industry. The results provided insights into the current status of QSP, future opportunities, and barriers that may impede its impact in pre-clinical studies.[9]

QSP Modeling Across All Stages of Model Initiation

Stage of model initiation and number of respondents:



Source: *CPT Pharmacometrics Syst Pharmacol.* 2018; 7(3), 135-146.

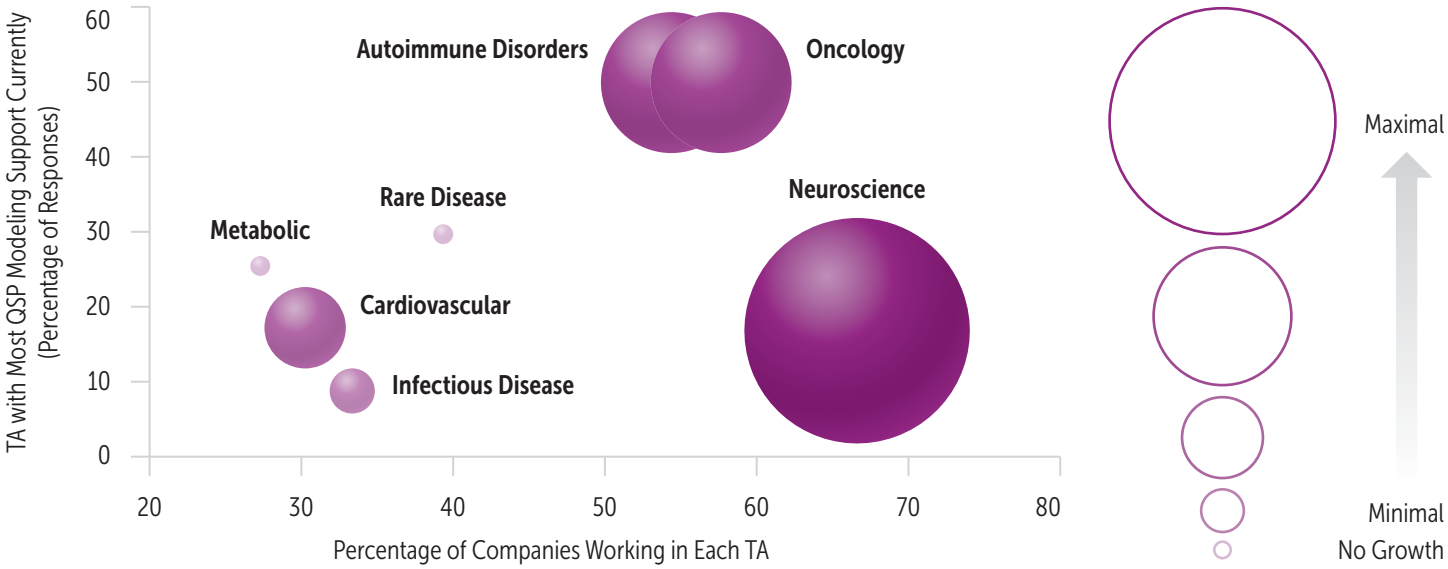
Findings from the International Consortium Survey

The Use of QSP Pre-clinical Modeling by the Pharmaceutical Industry

1. *QSP models are used across all stages of drug discovery and development—from before the selection of clinical candidates to interpret pre-clinical datasets, to informing biomarker translation, and supporting clinical development of drug candidates.*
2. *Oncology and immunology have been the most important therapeutic focus for QSP—neuroscience represents a future potential for QSP support.*
3. *There is a clear need to have a better definition and terminology around QSP—education will play a critical role in developing a consensus for its future use and communication.*
4. *QSP will become more impactful for critical decision-making and inclusion into regulatory submissions when pre-clinical QSP models are implemented in drug discovery.*

Current and Future Impact of QSP Across Therapeutic Areas

Source: *CPT Pharmacometrics Syst Pharmacol.* 2018; 7(3), 135-146.



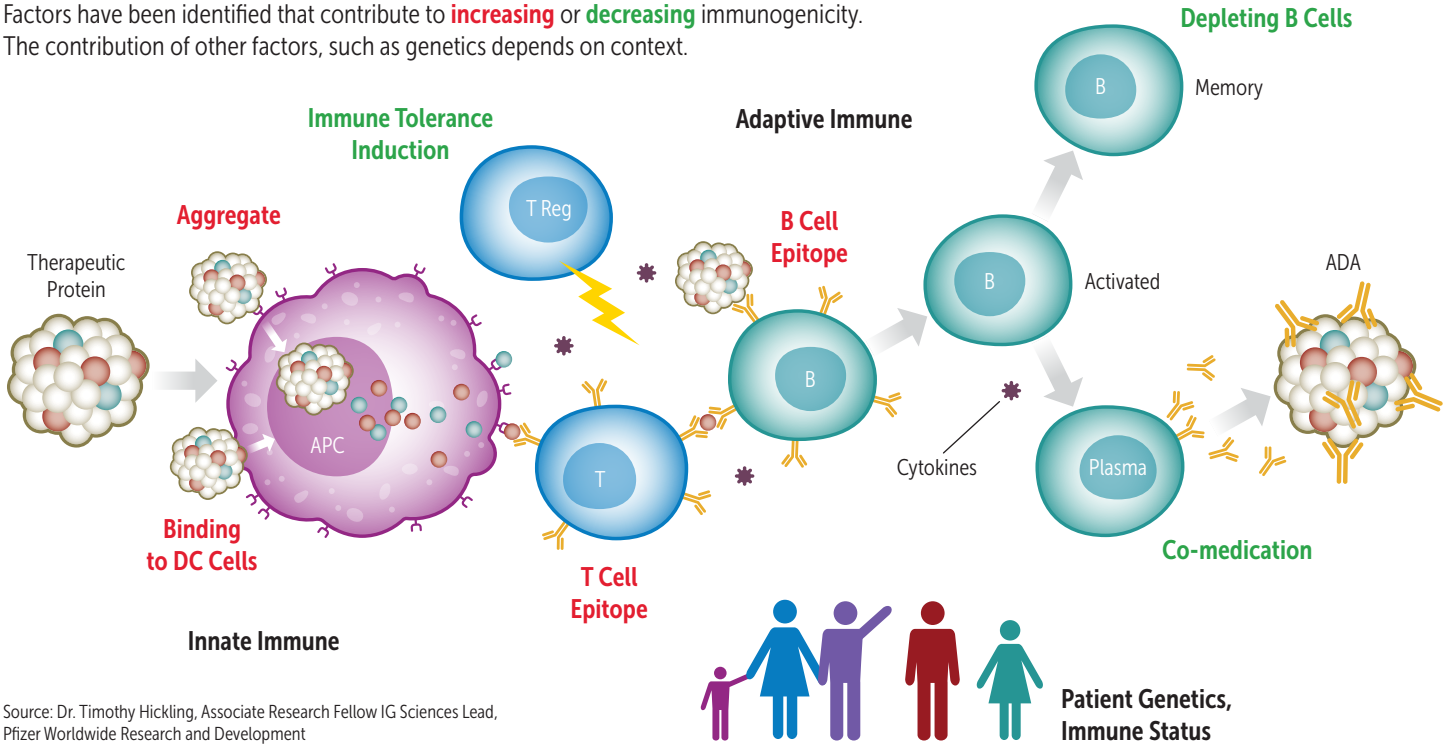
QSP has begun to gain regulatory and industry acceptance, analogous to the status of PBPK a decade ago. Today, regulators have embraced PBPK as both a discipline and as an integral part of company filings. The FDA published the use of a QSP model for the first time in 2014, which connected bone turnover markers with bone mineral density. Using this QSP model led the FDA to propose a different dosing regimen for a biologic from what the sponsor had proposed.[10] The EMA has also published its support of QSP models in the design of first-in-human trials.[11] Thus, similar to how mechanistic PK modeling has become an expected component in regulatory submission, it is anticipated that with increasing examples of using QSP to evaluate complex, heterogeneous diseases such as cancer, immunological, metabolic, and central nervous system diseases that require multiple therapies, it is anticipated that QSP modeling may follow the same trajectory as PBPK.

Using a Quantitative Modeling Approach to Better Understand Immunogenicity

Despite being "biological," most therapeutic proteins are synthetic—even fully humanized biologicals exhibit properties that can potentially be recognized as "non-self" and therefore have an increased risk of promoting an antigenic response. Although IG is clearly an important issue, the understanding of the phenomenon is limited. According to Dr. Timothy Hickling, Associate Research Fellow IG Sciences Lead at Pfizer, a big gap in understanding IG has been trying to determine how therapeutic proteins interact with the body's immune system. When he first became involved in the field of immunogenicity eight years ago, "sporadic information on IG existed, and most investigators pointed to risk factors, derived from their experience with individual products, where a product seemed fine and maybe there was a change in the product or of some characteristic of that product that caused unwanted immunogenicity. In addition, less sensitive or less drug-tolerant anti-drug antibody assays caused the true extent of immune responses to be overlooked. This led to a gap between the potential impact and measurement of IG and questioned whether IG was important, and if it was responsible for the effects being observed. As sensitivity and drug tolerance of assays improved, the relative observed incidences of IG increased, even on marketed products."

Factors Contributing to Immunogenicity

Factors have been identified that contribute to **increasing** or **decreasing** immunogenicity. The contribution of other factors, such as genetics depends on context.



Source: Dr. Timothy Hickling, Associate Research Fellow IG Sciences Lead, Pfizer Worldwide Research and Development

The IG response typically takes place in the form of the production of anti-drug antibodies (ADAs). ADAs may be an inevitable consequence of using biological drugs, but a given ADA level with respect to its binding may be manageable provided certain parameters are correctly optimized (eg, dose, frequency, route of administration, target patient population, tolerability strategy, co-medications). Finding the optimum for each drug will require a quantitative approach, hence the interest in QSP modeling.

In part, any immune response to a biological is an inherent property of the molecule itself and can be controlled to some extent. However, the data show that IG is complex and heterogeneous, depending, for example, upon the initial state of the immune system. This heterogeneity can be explained in large part by the fact that the immune response against biological agents is both humoral and immune-cell based and occurs via the innate, adaptive, and complement components of the immune system. These are highly complex interacting systems and can give rise to a range of outcomes, depending upon initial state and individual circumstances. Thus, the state of the patient's immune system and genetics at the individual level may be an important factor in IG.[12]

A further level of complexity is that the understanding of the impact of ADAs on drug pharmacology is limited. ADAs to mAbs are usually anti-idiotypic antibodies that target the drug binding site, as these are recognized as not belonging to the endogenous immunoglobulin repertoire of the host. Hence, ADA's tend to neutralize the intended pharmacology, which could in principle be surmounted at least to some degree by increasing dose. However, this must currently be dealt with in a bespoke, reactive, and data-driven manner that is both expensive and inefficient. Furthermore, ADAs are a heterogeneous population according to affinity, isotype, and neutralizing ability. ADAs may develop early while clinical efficacy is still present, be present at low levels, exist only within immune complexes, or be transient. Finally, non-neutralizing ADAs are possible, and the impact of these on drug PK/PD can be hard to predict. Improved quantitative understanding of these aspects of IG will be critical to improving the development of biological drugs.

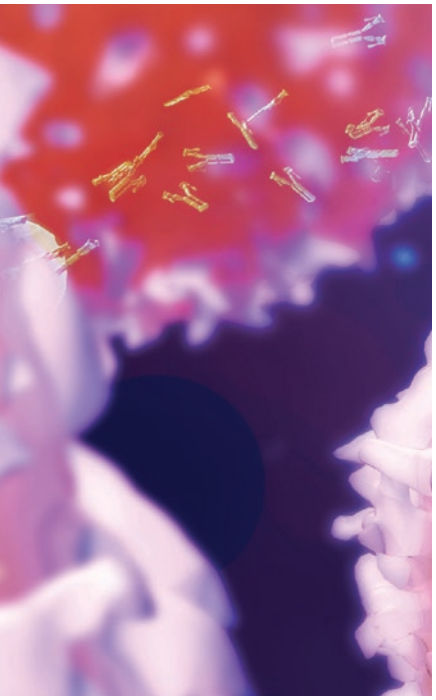
Other factors that contribute to the complexity of IG include the route and frequency of drug administration, the duration of treatment, formation of aggregates, and the co-administration of immunosuppressive agents. The potential for the formation of protein aggregates is an important issue for quantitative prediction of IG.[13] Immune complexes can be either small, which are cleared rapidly from the system, or large, which persist longer. Since different sized complexes will vary with individuals, the potential for varied PK outcomes and immune complexes may also have implications for safety. Quantitative predictions of the impact of aggregates on the PK/PD of biologicals will help to manage the risks associated with this behavior. When immunosuppressive agents, eg, methotrexate, are co-administered, the immune reaction against the therapeutic protein is reduced—evaluation of combination PK/PD of biologics with immune-suppressive agents will be necessary to optimize combination therapies.[14]

Factors that contribute to immunogenicity:

- Complexity and heterogeneity of the biological molecule and the state of the person's immune system and genetics at the individual level
- Recognition of biologicals properties as "non-self"
- Inability to properly predict drug PK/PD upon the production of anti-drug antibodies (ADAs) and non-neutralizing ADAs
- Route and frequency of drug administration, duration of treatment, co-administration of immunosuppressive agents, and formation of aggregates

Using QSP Models to Predict and Manage Immunogenicity of Therapeutic Proteins

It has been reported that the development of IG to treatment with a biologic range from mild transient antibody response (with no apparent clinical manifestation) to life-threatening reactions can have a profound effect on clinical outcome with reduced efficacy.[15] The high prevalence of IG not only impacts the clinical utility of existing treatments for patients but also the development of novel biologicals. This latter issue is exacerbated by the fact that IG often manifests itself relatively late in the drug development cycle, where the economic impact of attrition is at its greatest. Despite advances in the development of assays and techniques to assess IG at various stages of biological drug discovery and development, it is notoriously difficult to predict, and it seems unlikely that the occurrence of IG in clinical development will be dramatically reduced by modification of drug properties in the foreseeable future. Therefore, it can be concluded that IG will be associated with an increasingly large proportion of the global pharmaceutical development portfolio and will feature as a significant and recurring topic in interactions between pharmaceutical industry sponsors and regulatory agencies.



The focus of these interactions will be on how IG can be managed, rather than avoided. Thus, clear parallels can be drawn with more established areas of small-molecule clinical pharmacology and regulatory practice as such and the management of PK and PD variability in diverse patient populations, and specifically how MIDD has become a key enabler in this area.[16] Although empirical modeling approaches have been shown to be useful to quantify the impact of IG on PK, due to the complexity of IG, it is envisaged that a mechanistic QSP approach is required not only to develop our understanding of the issue but, importantly, to also manage it in the context of drug development and decision-making.[17] According to Piet van der Graaf, VP of Quantitative Systems Pharmacology at Certara, "while PBPK models depict ADME processes, QSP models add in biological pathways that are relevant for disease modification."

Prediction of likely ADA response prior to clinical use of a drug has been explored using animal models. However, to date, the predictive utility of pre-clinical animal models has been limited.[18] In part, this is due to the candidates often being "humanized," and therefore hard to study meaningfully in animals, and the much documented difficulties in interpreting how good or otherwise any animal is as a representation of the human immune system. This is unlikely to be solved in the near term and therefore an alternative approach is needed.

Given the complexity of processes involved in IG, the development of quantitative, mechanistic models of humoral and cellular responses involved in IG will be invaluable in supporting both development decisions and the regulatory approval process. Currently, modeling of IG focuses on machine-learning approaches to predict IG directly from sequence. Not surprisingly, this is insufficient as it does not take into account the full complexity and dynamics of humoral and cellular responses, let alone the baseline differences between individuals within the clinical population. Crucially, current approaches focus on an attempt to avoid IG, which will not be generally possible, rather than managing IG through dose, route of administration, selection of patient population, tolerance, or the impact of co-medications. Consequently, antigenic propensity calculated from sequence is a useful input into a dynamic model, alongside *in vitro* assay data, rather than the metric to be directly used for development and regulatory decision-making.

In the absence of being able to generate easily interpreted pre-clinical animal model data and the requirement for quantitative rather than qualitative input, the options for tackling IG would appear to be limited. However, the mechanistic elements of the immune biology are understood to a useful extent and can be informed with human patient input data from clinical and potentially *in vitro* and *ex vivo* sources. Theoretical mechanistic multiscale mathematical models of IG represented by the subcellular, cellular, and whole-body levels have been developed, which can serve as good starting points.[19]

A software tool capturing this mechanistic understanding of the immune biology that can simulate virtual populations with inter-individual variability based on input data will enable an improved clinical development path for biologicals. Optimal dosing routes and regimens can be explored in virtual populations giving input to likely success rates for given biologicals and patient populations. Early emerging clinical data can be included, such as PK profiles matched with ADA titers and drug affinity (KD), enabling optimal decision-making regarding dose and enriching the quality of the models. With rich clinical data, the confidence in the tool predictions can be verified, and scope and mechanistic detail optimized, potentially enabling increased understanding of key IG processes and biomarkers. As Hickling points out, "There are more things we can measure earlier on to give us a better indication, but ultimately we want to say 'this is how the immune systems works.'

As long as we can get sensitive assays that better discriminate between a weak and very weak antigen, then we should be able to project whether the impact's going to occur at one or five years. That's going to make a massive difference to commercial decisions that are perhaps being made at the end of a Phase 2 study."

Creating a Consortium: Tackling Immunogenicity through Expertise and Cooperation

Capturing existing knowledge and translating it into a mechanistic modeling platform is a resource intensive process that would benefit from a team of experts working collaboratively and in a pre-competitive arena. A platform designed in a modular way, which allows modeling of competitive compound data and models in the full context of the mechanistic knowledge on humoral and cellular immune response, is an objective end-point.

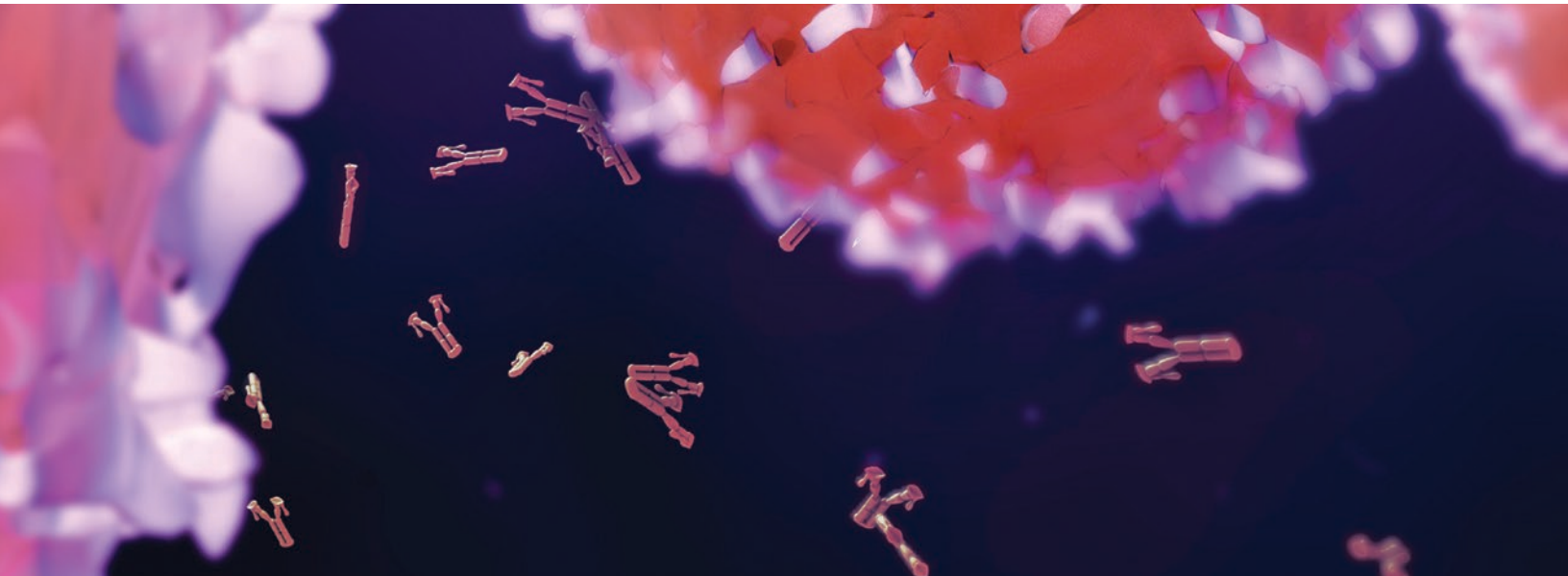
Certara formed a QSP IG Consortium in 2017 that brings together leading biopharmaceutical companies in a pre-competitive environment to cooperatively develop an Immunogenicity Simulator based on state-of-the art QSP science and methods. The IG Simulator will predict IG and its impact on compound PK, efficacy, and safety in diverse patient populations in drug discovery and development. The IG Consortium is the first of two QSP-focused Consortiums formed by Certara—the second, the QSP Immuno-oncology Consortium, was formed earlier this year to cooperatively develop a QSP Immuno-oncology Simulator that can model clinical populations of cancer patients. According to van der Graaf, better predictive approaches are needed for immuno-oncology combination therapies. "It's incredibly difficult—if not impossible—to predict the level of combination synergy without having a quantitative model."

The QSP IG Consortium is modeled after Certara's highly successful Simcyp Consortium, whose members use the Simcyp Simulator PBPK modeling and simulation platform to select the most appropriate drug doses, design optimal clinical trials, evaluate new drug formulations, and predict drug-drug interactions (DDIs) and PK outcomes in clinical populations.[20] Simcyp provides high-quality, systematic, critically reviewed, and comprehensive coverage of original scientific literature—an approach that Simcyp has used to translate literature knowledge into regulatory-standard population PBPK models and software, and one which will be carried through with the IG Simulator.

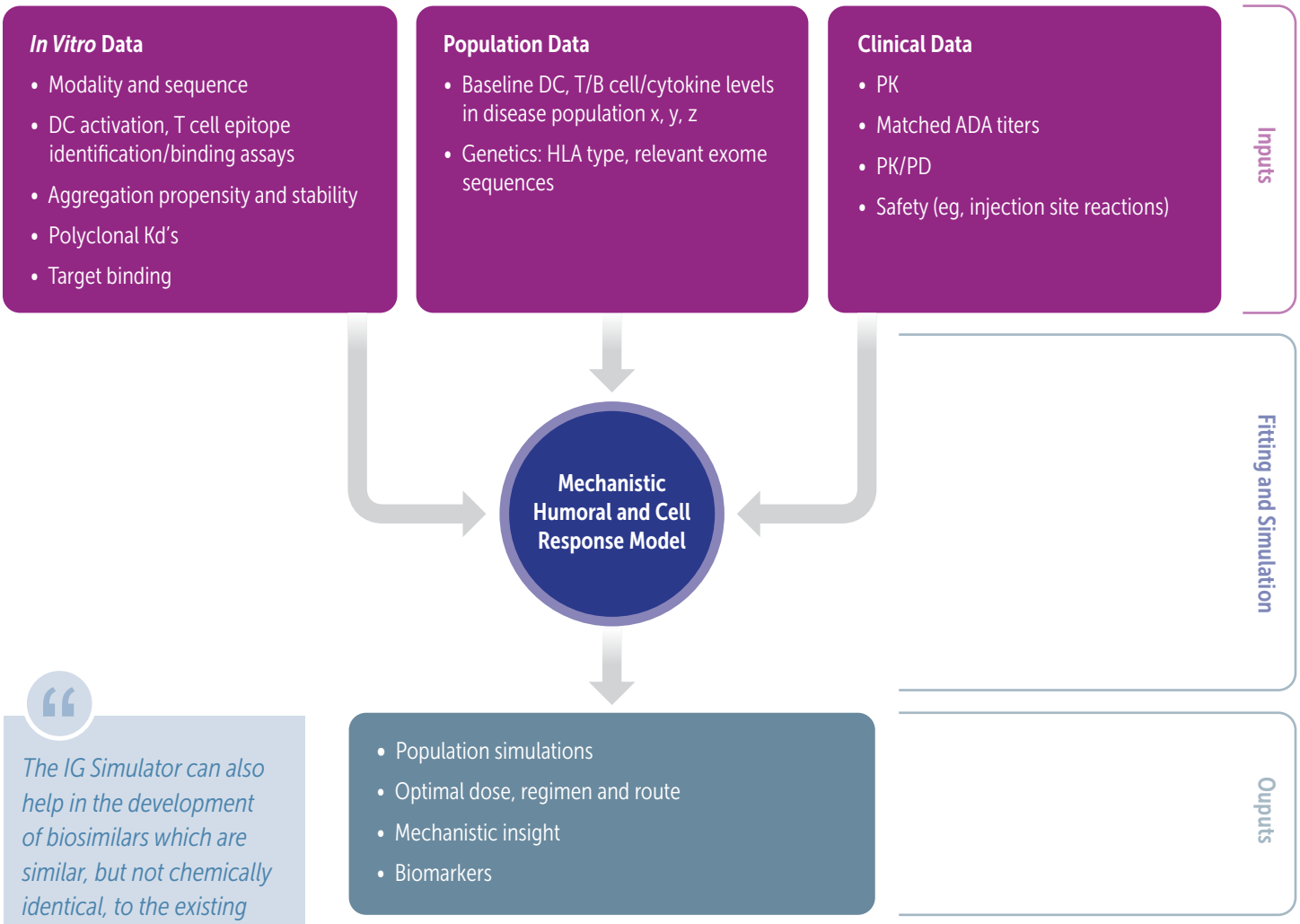
The QSP Consortium will use a variety of structural, *in vitro* and *in vivo* input parameters to develop dynamic models, which will be implemented in a robust IT platform coupled to a virtual patient simulator that can be used to make development and regulatory decisions.

The IG Simulator will facilitate incorporation of input data including modality and sequence, *in vitro* assays of DC activation, T cell epitope identification/binding, population baseline immune status, genetics, and drug clinical PK/PD data. This tool can then be used to more rationally and quantitatively explore the likelihood of IG from the pre-clinical stage of drug development. The ability to incorporate clinical data enables the extension of learn-confirm cycles into Phase 1, 2, and 3 stages of clinical development, thus giving the potential to not only optimize dose, route, and regimen, particularly critical for special populations, but also to build confidence in the models.

The QSP IG Consortium will create a critical mass of expertise and experience (biocuration, system modeling, software development, inter-company immunology expertise) and experimental data to create a comprehensive, bottom-up, literature-based mechanistic model of humoral and cellular immune response to biologic drugs and provide this model in a software platform developed with an eye on regulatory quality standards.



High Level View of the IG Simulator: Mechanistic Structure, Inputs, and Outputs



> *The IG Simulator can also help in the development of biosimilars which are similar, but not chemically identical, to the existing innovator product. Since biosimilars are not identical to the reference product, they cannot be directly substituted, and they may display different IG responses. The IG Simulator can inform optimal design for biosimilar products and minimize or perhaps even replace clinical studies needed for approval.*
>
> – Piet van der Graaf

Moving Towards Better Prediction and Management of Immunogenicity in Biologics Drug Development Using a QSP Approach

Mechanistic modeling has become a standard across the drug development continuum and an expected component of regulatory submissions. The rapid rise of biologics drug development with the development of immunogenicity to treatment a major factor affecting efficacy and safety of biologics, and a key area of regulatory interactions for this class of drugs, is evident that a quantitative approach can be used to help to better predict and manage IG. The IG Simulator can also help in the development of biosimilars which are similar, but not chemically identical, to the existing innovator product. Since biosimilars are not identical to the reference product they cannot be directly substituted and they may display different IG responses. The development of a robust IG Simulator by a pre-competitive consortium based on state-of-the art QSP science and methods to predict IG and its impact on compound PK, efficacy and safety in diverse patient populations will be a valuable tool for the biologics drug development and regulatory submission.

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