CERTARA®

Advancing Innovation in Drug Development and Patient Care

2019 Best of Blogs

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Introduction

The difficult we do immediately, the impossible takes a little longer.

- Charles Alexandre de Calonne, 1974

At Certara, we dream big. We're driven by our mission to use innovative technology to help our clients develop safer, more effective therapies that address unmet medical needs.

And it's a good thing we dream big because developing drugs and getting them to patients often feels close to impossible. There are so many hurdles to clear: generating the scientific evidence to achieve regulatory success, striking the right risk-benefit profile for patients, standing out from a fierce pack of competitors, and communicating value to payers.

We're proud to have completed our fifth year of blogging. Five years of telling you our biggest challenges and accomplishments in model-informed drug development, health economics/outcomes research and real world evidence, and regulatory science, strategy, and services. Our most exciting stories of 2019 are captured in this blog book. Remember to visit us online at Certara.com and share with us your comments on the evolving landscape for drug development and patient access.

Happy reading!

Suzanne Minton, PhD
Certara Blog Editor-in-Chief

CERTARA®

Innovations in Drug Development

At Certara, we are innovators, dedicated to helping our clients develop new therapies and target unmet medical needs, expand existing therapies to other subpopulations, communicate scientific information in the language of regulatory success and market access, balance risk-benefit profiles, differentiate therapies from the competitive landscape, and unlock millions of dollars in R&D savings.

Our modern, state-of-the-art integrated drug development approach uses quantitative methods to inform, guide, and supplant traditional development methods while dramatically improving efficiency and reducing costs. Creating unquestionable value for our clients is our objective.

The blog posts in this section address how Certara is using innovative approaches to tackle some of the biggest problems in pharma including supporting global health, developing safer, more effective medications for children, and tackling complex drug safety issues such as immunogenicity.

Certara Scientists Support TB Alliance's Groundbreaking New Drug

David Salinger | Ellen Leinfuss

08.29.2019

On August 14, the FDA approved the anti-TB drug pretomanid, only the third new drug for tuberculous (TB) in almost 50 years. Pretomanid's developer, TB Alliance has become the first not-for-profit organization to both develop and register an antibiotic. The approved label provides for the use of pretomanid as part of a combination regimen with bedaquiline (Janssen) and linezolid (Pfizer), for the treatment of adults with pulmonary extensively drug-resistant TB (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) TB. Pretomanid is the first-ever US FDA-approved drug for XDR-TB. The TB Alliance, which is dedicated to finding faster-acting and affordable drug regimens to fight TB, operates with the support of an extensive list of government and philanthropic organizations.

Powerful New Results from this New Therapy

According to the World Health Organization, TB kills 1.6 million people a year, about 500,000 of whom suffer from drug-resistant strains of the disease. Common TB treatments are ineffective for patients with XDR-TB. The standard of care for patients with this extreme form of the disease can include a combination of eight drugs for 18 months or more. However, the drugs can come with serious side effects, such as deafness, and up to two-thirds of patients with XDR TB are not expected to survive.

In a clinical trial for extensively drug-resistant (XDR) TB and treatment-intolerant or nonresponsive multidrug-resistant (TI/NR-MDR) TB, approximately 90 percent of patients receiving this newly approved regimen recovered after six months of treatment —almost three times the success rate of prior treatment options. This groundbreaking work also resulted in the award of a tropical disease priority review voucher and sets the stage for a new approach to creating the next-generation of antibiotics for neglected diseases like TB.

Certara's Participation in this Program

Certara is honored and humbled to have participated in this novel development program providing scientific support to the TB Alliance and the Bill & Melinda Gates Foundation during the development and regulatory filing processes. Certara contributions included population pharmacokinetic (PK) modeling, QTc (cardiac safety) modeling and analysis, PK/PD (pharmacokinetic/pharmacodynamic) modeling and related dataset construction in support of early decision-making and the regulatory submission.

Peer reviewed publications have already resulted from the contributions[1,2,3], with other manuscripts in process.

Certara is a Mission Driven Organization

About 6 weeks ago, we shared the launch of Certara Global Health and the expansion of our work with the Bill & Melinda Gates Foundation. Today's news is another example of our contribution to achieving equity in health for all people worldwide.

In fact, in the past year or so, our contributions to global health have included:

1. Certara's collaboration with Medicines Development for Global Health (MDGH) on its new drug approval for moxidectin for treating river blindness,[4] a neglected tropical disease. Like today's news of this new TB treatment, MDGH was awarded a tropical disease priority review voucher, which was recently sold to

Novo Nordisk so that MDGH can continue to develop treatments for neglected diseases.

2. Certara's scientific support to Siga for the development of TPOXX (tecovirimat), the first drug with an indication for treatment of smallpox.[5] Siga is focused on providing solutions for unmet needs in the health security market that comprises medical countermeasures against chemical, biological, radiological, and nuclear (CBRN) threats, as well as emerging infectious diseases.

Though the World Health Organization declared smallpox, a contagious and sometimes fatal infectious disease, eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon. According to the FDA, "This is the first product to be awarded a Material Threat Medical Countermeasure priority review voucher. Today's action reflects the FDA's commitment to ensuring that the U.S. is prepared for any public health emergency with timely, safe and effective medical products."

- The selection of Certara by the Centers for Disease Control and Prevention (CDC) to develop a technology platform to strengthen the agency's death investigation and surveillance systems.[6] The technology we are creating will aggregate disparate data in a secure and private structure to facilitate decision-support analysis, visualization, and reporting of toxicology and other key drug-induced death information to address the drug overdose crisis in this country.

Under contract to the Australian Government, Certara drafted a report and plan, entitled "Medical Countermeasures Initiative: National Capability Audit 2017".[7] This audit, and reports building from it, provides a framework for Australia to prepare and contribute to the global efforts in medical countermeasures product development.

Triple Bottom Line

The triple bottom line (TBL) is a concept that broadens a business's focus on the financial bottom line to include social and environmental considerations. While today's news and the examples shared above provide a clear example of Certara's TBL commitment, our work every day in support of the development and patient access to safer and effective therapies underlies our mission.

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Trial Simulation: An Innovative Approach to Assess Pediatric Drug Dosing

Edward Nehus

01.11.2019

As a pediatric nephrologist, I help care for some very sick kids. And because our young patients are so ill, it's a challenge to recruit them into clinical studies. Of course, we want to provide our patients with the best care; getting the dose right on their medications is a big part of that. However, variability in both demographic (age, weight) and clinical factors like receiving continuous renal replacement therapy (CRRT) can alter drug pharmacokinetics (PK). *In silico* approaches like computer-assisted trial design can help us to assess which dosing regimens are most likely to achieve target attainment while minimizing the risk to pediatric patients. In this blog, I'll discuss the clinical situation that led us to use Certara's Trial Simulator to model dosing of an antibiotic in children with acute kidney injury who are receiving CRRT.

Sepsis: Still a Major Cause of Pediatric Mortality

Sepsis is a prevalent cause of acute kidney injury in children that may require CRRT. You can think of CRRT as a continuous form of dialysis. The outcomes in this population show critically ill children who are receiving CRRT have mortality rates exceeding 40%.[1] Inadequate treatment with antibiotic therapy is predictive of patient mortality.[2] So it's critical to adequately dose potentially life-saving antibiotics in this population. Meropenem is a potent, broad spectrum antibiotic that is frequently prescribed in this population.

Meropenem PK

Let's briefly review the pharmacokinetic properties of meropenem. It is primarily excreted by the kidneys[3] and is characterized by time-dependent bactericidal activity. Thus, meropenem's efficacy is determined by the percentage of time during the dosing interval that the concentration of free drug in the serum exceeds the minimum inhibitory concentration (MIC) for the targeted bacterial agent. And the MIC is the minimum amount of drug necessary to prevent bacterial growth on a petri dish.

The characteristics of meropenem render it significantly removed by CRRT. It has a small volume of distribution, insignificant protein binding, and has a small molecular size.

Principles of CRRT

To understand how we incorporated CRRT into the model, I'll explain how it works at a high level. The CRRT machine is hooked up at the patient's bedside. It contains a filter to clean the blood. Then a patient would typically have a catheter inserted at an internal jugular vein. Their blood would flow through an access line and then circulate through the filter and then return to the patient through a return line. Blood is cleaned by additional fluid that runs through the machine, mixes with the blood, and is then removed. This process clears the patient of toxins that build up in kidney failure. The total dose of CRRT is typically represented by the total amount of fluid that is collected by the machine, expressed in mL/hr.

PK in Patients Receiving CRRT

Understanding the pharmacokinetics of medications in critically ill children is challenging for multiple reasons. First, pediatric patients with sepsis can have alterations in their PK compared to healthy children. For example, they can have an increased volume of distribution. That can be due to capillary leak associated with the inflammation itself or to receiving excessive amounts of resusci-

tative fluids. Also, they can have acute kidney injury which can affect the clearance of renally cleared drugs. And this population has documented inter-individual variation in PK parameters. In addition, CRRT itself affects drug clearance. It removes drugs smaller than a certain size including meropenem.

The main CRRT dosing prescription parameter that affects drug clearance is the total effluent volume.

In summary, CRRT dosing and prescription differences can affect drug pharmacokinetics. These alterations in PK can then influence the optimal dose to give to these pediatric patients.

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The Role of Quantitative Systems Pharmacology in First-in-Human Trial Design

Piet van der Graaf 04.26.2019

Quantitative Systems Pharmacology (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 combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. QSP has already shown promise for increasing the probability of success in R&D by bridging scientific gaps between disciplines to enable target validation and is recognized by sponsors and global regulatory agencies as a valuable scientific approach to increase understanding of disease biology, improve target selection, and help to ensure drug safety and efficacy in clinical trials.

Why Use QSP for First-in-Human Trials?

QSP can also be used in the efficient design of First-in-Human (FIH) clinical trials to help determine the starting dose and subsequent dose escalations to ensure the best possible protection for human subjects. If FIH doses are estimated only on the basis of preclinical data, without including mechanistic model-based approaches such as QSP, investigators are not making the best use of all available data.

A Review of the Endocannabinoid System for Treating Pain: A Prelude for Endorsing the Use of QSP in FIH Studies

The endocannabinoid system (EC) is involved in many physiological processes in the central and peripheral nervous systems such as pain, sensation, appetite, mood, and memory. Modulating EC system activity has been investigated by the pharmaceutical industry for its potential to treat a wide range of diseases including neuropathic pain, cardiovascular diseases, Parkinson's and Huntington's disease, and many others. The identification of cannabinoid receptors, CB1 and CB2, belonging to the superfamily of G protein-coupled receptors (GPCRs), and their endogenous lipid ligands, spurred research into therapeutic compounds that inhibit EC metabolism and transport, e.g. fatty acid amide hydrolase (FAAH), a membrane-bound serine hydrolase which degrades endocannabinoids in the brain.

Historically, FIH studies and early stage clinical trials have been conducted with a notable safety record. However, the 2016 tragic outcome of the FIH trial on BIA 10-2474, a FAAH inhibitor, which led to the death of one volunteer and produced mild-to-severe neurological symptoms in four others, resulted in the European Medicines Agency (EMA) revising their guideline on pre-clinical and clinical aspects of FIH and early clinical trials. Although the clinical neurotoxicity is still unclear, activity-based protein profiling studies to determine the protein interaction landscape of the test compound in human cells and tissues has shown that the high doses of BIA 10-2474 administered may have attributed to off-target activities of BIA 10-2474 leading to severe adverse effects.

Incorporating a QSP Approach to FIH to Avoid Severe Adverse Outcomes in FIH Trials

Last year in a Clinical Pharmacology and Therapeutics (CPT) Letter to the Editor, we proposed that if a QSP modeling approach – that complements conventional pre-clinical standards in translational drug development – was used in the BIA 10-2474

FIH trial, the disastrous outcomes of the trial could have been avoided. QSP modeling would have provided a more meaningful prediction of the pharmacodynamic range and maximum dose for the BIA 10-2474 FIH than pre-clinical animal data.

The CPT letter illuminates how while the EMA and the pharmaceutical industry agree on how the new guideline emphasizes the better use of pre-clinical data to guide rational dose selection of FIH studies, they differ in their perspective on defining the pharmacodynamic range and maximum dose that can be explored in a FIH study. The industry and regulatory view suggests that FIH doses can only be estimated on the basis of pre-clinical data. This stance ignores the promising role of using QSP, and other mechanistic modeling approaches, which may or may not use pre-clinical data.

To validate the value of incorporating a QSP approach for the BIA 10-2474 FIH trial, we highlighted the results of a QSP model we published in 2014 that identified gaps in the field's understanding of the pathway. Our model helped explain why the selective FAAH inhibitor PF-04457845 failed in Phase II testing by Pfizer for osteoarthritic pain. In the absence of relevant pre-clinical animal models of pain, the QSP model was entirely based on and calibrated against *in vitro* and human literature data. In the PF-04457845 study, the QSP model predicted a limited modulation in the brain of the target of interest CB1 – the magnitude of which would saturate at relatively low doses of the test compound. Based on similarity of the biomarker anandamide data from both the PF-04457845 and BIA 10-2474 studies, the QSP model's conclusions in the 2014 FAAH inhibitor study could have forewarned that the high daily dose of BIA 10-2474 was beyond what was needed to saturate the target pharmacology.

The Future of QSP in FIH Studies

We believe that mechanistic models complement conventional pre-clinical standards in translational drug research and should be more widely adopted by drug developers, encouraged and supported by regulators, and included in future guidelines. In the response to our CPT Letter to the Editor, regulators in the EMA "welcomed the initiative shown" and stated, "Mechanistic models leading to further refinement of the predictions from standard pre-clinical procedures and the use of additional drug-specific or mechanistic data or considerations are encouraged. Relevant models holding the potential to better reflect a substance's effects in human tissues and potentially improve the safety of trial participants will be supported by the EMA."

At Certara, we routinely employ QSP models – modular in form and extendable whenever new biological insights become available – to support clinical trial designs for a variety of mechanisms and indications. Our two QSP consortia— on immunogenicity and immune-oncology— represent members from leading biopharmaceutical companies who will help to continue and advance the development of QSP models for drug development.

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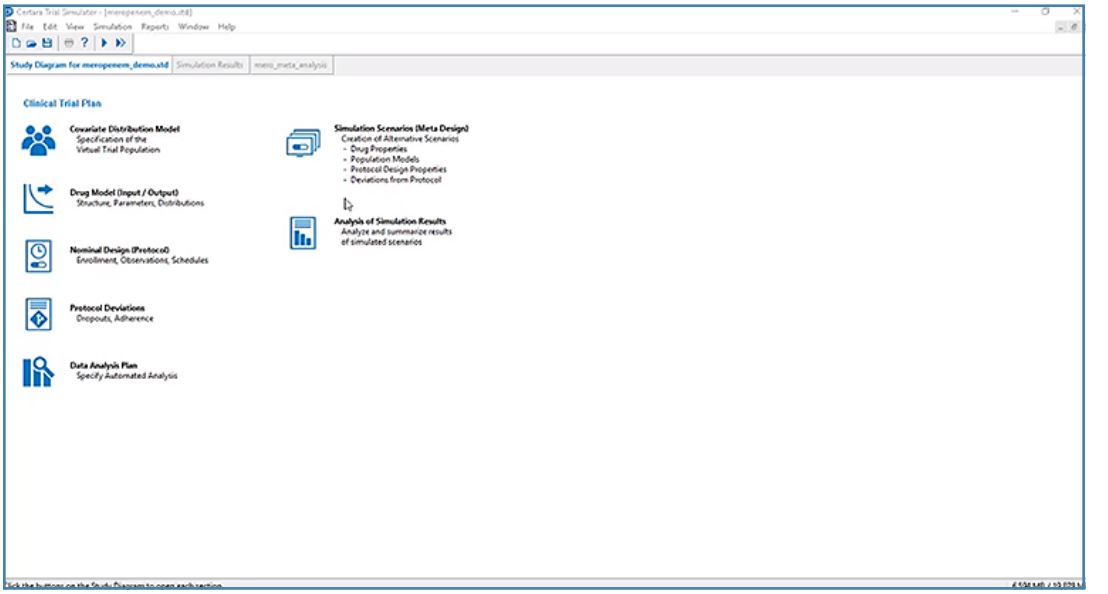
A Beginner's Guide to Performing Clinical Trial Simulation Using Technology

Mark Lovern 02.08.2019

The astronomical cost of conducting clinical drug trials means that a suboptimal trial design adds significant risk to a drug program. Clinical trial simulation allows drug developers to test different trial designs *in silico* before exposing patients to an experimental drug. In this blog post, I'll explain how Certara's Trial Simulator balances ease-of-use with robust tools for defining study design attributes, conducting statistical and sensitivity analysis, and creating graphical summaries to plan effective trials for every phase of clinical drug testing. As an example, I'll discuss a previously published Trial Simulator model[1] that was developed to evaluate the probability of target attainment for various antibiotic dosing regimens in a range of ages and fluid overload levels in pediatric sepsis patients with acute kidney injury who are receiving continuous renal replacement therapy (CRRT).



This is the main dashboard for Trial Simulator. Its icons are arranged in an order that make sense as you're thinking about conducting a clinical trial simulation.

Specifying the Virtual Trial Population

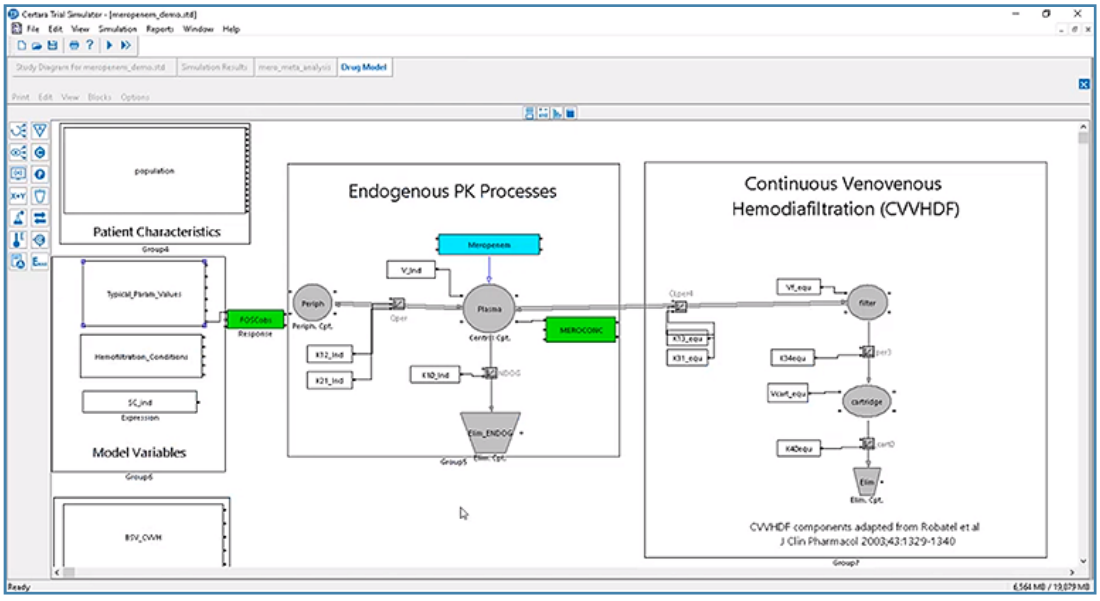
One of the first things to consider is the trial population. In this case, we're simulating a pediatric population. In addition to the individual

patients' physiological characteristics, we need to include characteristics regarding their CRRT.

For covariate distribution, specify the individual patient characteristics (parameters such as age, body weight, gender, etc.) to be available to the drug model. While I can use parametric simulation for covariate distributions, it's generally better to use real world data because it preserves the inherent correlations between characteristics like body weight, age, gender, etc.

Developing the Drug and Disease Models

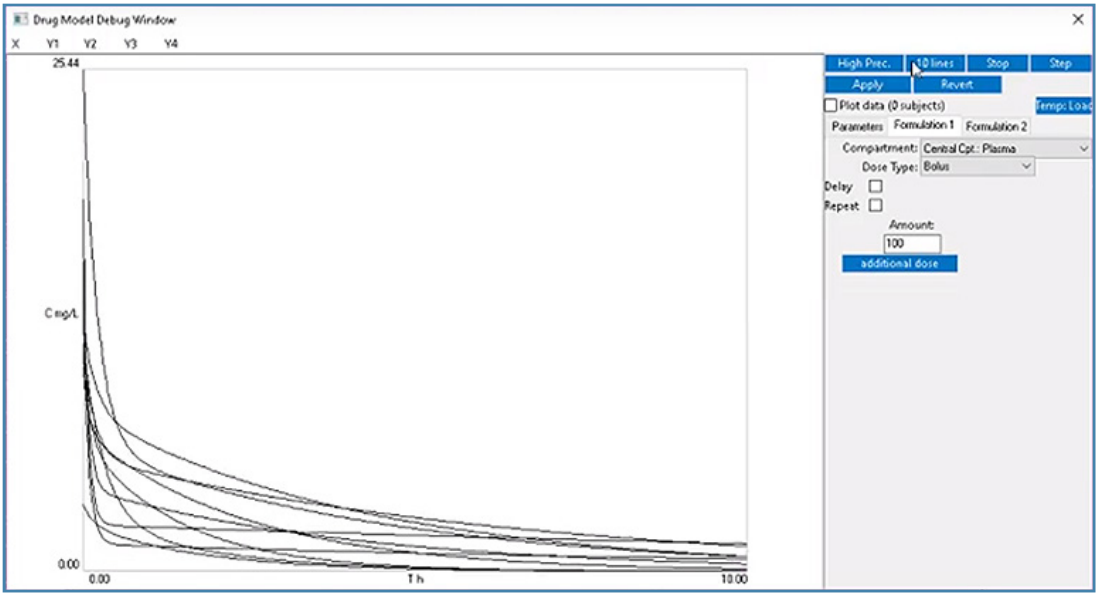
Now that we've specified the characteristics of our patient population, let's talk about the drug and disease model. This is the model specification workbench that Trial Simulator uses; I've grouped the model components into two categories.



On the left are the variables that the model will pull in and use as needed. These variables can be from the literature or user-specified. The middle block describes endogenous pharmacokinetic (PK) processes including the dosing of the antibiotic, meropenem, into the central compartment via IV administration. This two-compartment model has between subject variability on all parameters. The model includes some natural elimination of drug. However, patients with sepsis often experience renal impairment. So on the right are the model parameters and processes associated with CRRT.

Drug Model Debug Window

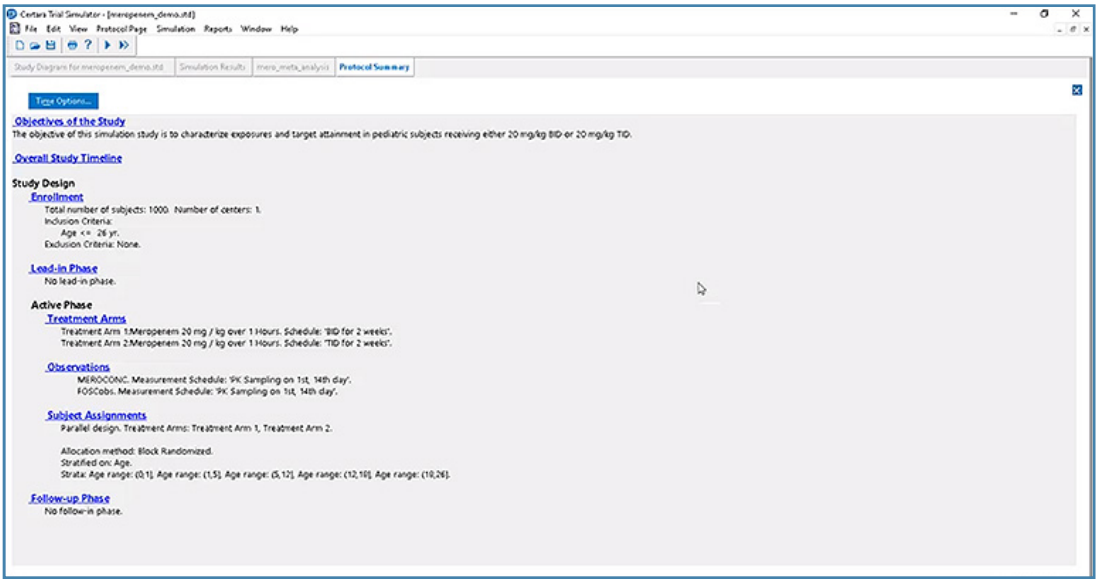
One way that Trial Simulator helps users build their models is the drug model debug window.



For instance, if I want to check that I've specified my model correctly, I can provide a dose to the model's central compartment. The debug window then generates the plasma drug concentration-time profiles for up to 50 individual virtual subjects. This visual aid lets me see how variable the simulated profiles are and detect any behaviors that may indicate model misspecification.

Designing the Trial Protocol

Now that we've specified our drug and disease model and our trial population, we will consider our trial design.



The interface for specifying the virtual trial design is similar to a clinical trial outline including the study objective, timeline, and design. For the study's enrollment, we're simulating large cohorts of subjects to make recommendations for the population as a whole. We're not necessarily evaluating the probability of trial success. If we were, we'd match the number of subjects to the intended design for the trial. And we could even explore the sensitivity of trial outcomes to varying the number of subjects.

The study timeline contains information pertaining to dose administration and sampling of endpoints. In this case, drug administration is either twice (BID) or three times (TID) daily. On day seven, PK samples to measure meropenem concentrations are taken. The study timeline also includes a fluid overload variable as subjects undergoing CRRT often retain water. Fluid overload impacts the drug's volume of distribution. By including this variable, we can explore the potential impact of increasingly severe states of fluid retention on PK.

In addition to the overall study timeline, we can specify the trial's treatment arms. Trial Simulator supports scaling the amount of drug administered by covariates, adjusting dosing using a covariate dose adjustment table, or adjusting dosing based on response values. For instance, if the trial was studying a diabetes drug, I could titrate the dose based on subjects' fasting plasma glucose.

When assigning subjects to treatment arms, you can stratify them based on a covariate such as age. We can also build a lead-in phase where the subjects receive a pre-treatment. Then they can be assigned to treatment arms based on their response to the pre-treatment.

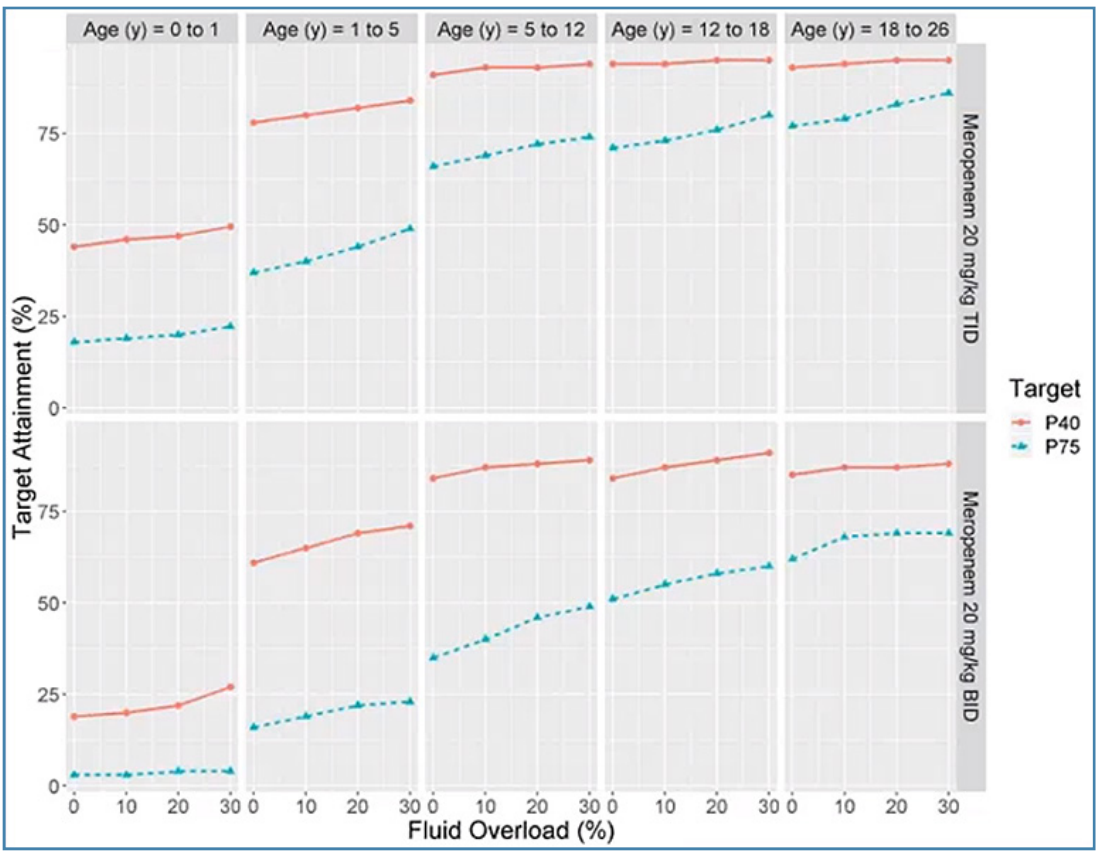
Protocol Deviations

When we design a trial, we assume that everything will follow the protocol. But, in real life, protocol deviations occur such as missed observations and patient non-adherence. Trial Simulator has capabilities to simulate protocol deviations like drug holidays.

Analysis Tools

Trial Simulator can analyze the data from a simulated trial using descriptive statistics, ANOVA/ANCOVA, or a custom analysis in R. For instance, I developed an R script that computes the target attainment rate for subjects based on their meropenem concentrations. One of the most powerful aspects of trial simulation is that you can test multiple scenarios with regard to your assumptions, the drug and disease model, and aspects of the trial design.

Here is a plot showing the target attainment rates for four different degrees of fluid retention for patients in each age group. Within each age group, we have the two treatment schedules and the two targets: 40% (P40) and 75% (P75) of the dosing interval has a plasma drug concentration above the minimum inhibitory concentration (MIC).



The top row of plots are for TID administration for meropenem while the bottom row is for BID dosing. The columns are the various age categories. For ages five and up, the subjects show high rates of target attainment, especially for the TID administration and the P40 target. However, for younger age groups, particularly for the BID administration, attainment rates are markedly lower. Thus, we can conclude that for younger patients, we likely need to give higher doses to achieve adequate drug exposure.

You should now understand some of the major principles of trial simulation, and why this approach can help to optimize trial design and maximize probability of success.

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Managing Immunogenicity in Biologic Drug Development

Piet van der Graaf 02.22.2019

The Challenge of Immunogenicity in Biologics Drug Development

Biologic drug development is a rapidly evolving sector in the biopharmaceutical industry. Biologically-based therapeutic drugs comprise monoclonal antibodies (mAbs), vaccines, recombinant hormones and proteins, antibody-drug conjugates, RNAi, antisense, blood factors, and other large molecules. 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. In a recent FDA review of 121 approved biological products, 89% of the products had reported immunogenicity, and in 49% of the cases, IG affected the drug's efficacy.

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. A big gap in understanding IG has been trying to determine how therapeutic proteins interact with the body's immune system.

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 (e.g., dose, frequency, route of administration, target patient population, tolerability strategy, co-medications). Finding the optimum parameters for each drug will require a quantitative approach, hence the interest in Quantitative Systems Pharmacology (QSP) modeling.

Quantitative Systems Pharmacology—Bridging Pharmacokinetics and Systems Biology

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 combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process.

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, confirm drug target binding and modulation, and as an approach that can affect preclinical development.

Using a Quantitative Modeling Approach to Better Understand Immunogenicity

Managing IG is a challenge not just in drug development but also in manufacturing and, in particular, patient care. In part, any immune response to a biological is related to the properties of the molecule itself and can be controlled by design to some extent. However, the data show that IG is complex and heterogeneous, depending, for example, upon the initial state of the immune system. Many factors contribute to the complexity of immunogenicity including (1) limited understanding on the impact of ADAs on drug pharmacology, (2) route and frequency of drug administration, (3) duration of drug treatment, (4) formation of aggregates, and (5) co-administration of immunosuppressive agents.

A QSP-based approach can be used to predict and better manage immunogenicity and guide clinical and regulatory decision-making in biologics drug development.

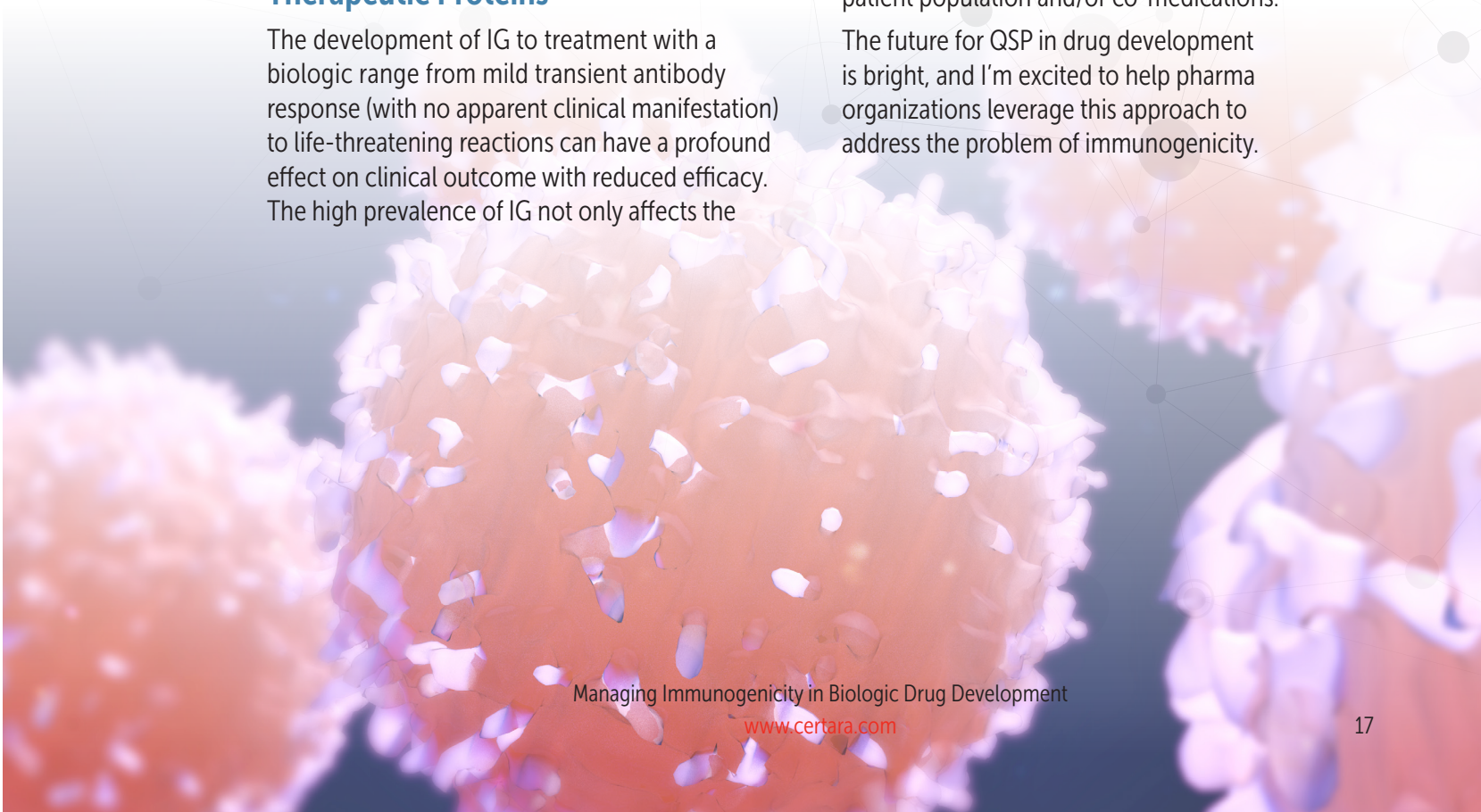
Using QSP Models to Predict and Manage Immunogenicity of Therapeutic Proteins

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. The high prevalence of IG not only affects the clinical utility of existing treatments for patients but also the development of novel biologicals. Therefore, 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. A mechanistic QSP approach is required to understand the issue and to manage it in the context of drug development and decision-making.

Creating a Consortium: Tackling Immunogenicity through Expertise and Cooperation

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. This new tool will enable sponsors to manage immunogenicity by adjusting the biologic dose, route of administration, patient population and/or co-medications.

The future for QSP in drug development is bright, and I'm excited to help pharma organizations leverage this approach to address the problem of immunogenicity.



Simulating Viral Dynamics in Virtual Patients

Suzanne Minton | Bill Poland 04.10.2019

Antiviral drug development presents a unique set of challenges. First, viruses are constantly mutating, and drug-resistant viruses emerge easily. Therefore, combination therapies are typically required to maintain a sustained virologic response. In addition, successful treatment requires high medication adherence, which is often a challenge for patients with chronic viral infections such as hepatitis or HIV. In this blog, we'll discuss how clinical trial simulation can support antiviral drug development by characterizing the dose-response relationship, quantifying the impacts of patient adherence, and simulating the probability of success for alternative trial designs. Certara's newly updated Trial Simulator can simplify building trial or population simulation models with built-in features that support pharmacokinetics (PK), pharmacodynamics (PD), adherence, and trial design modeling.

Viral Dynamics: What is it, and why Model it?

Viral dynamics (a.k.a. viral kinetics) refers to the mathematical description of the interaction of the virus and its target cells over time. One of the most important measures of viral dynamics is the basic reproductive ratio, R_0: the number of cases that one infected cell, or person, generates on average in an otherwise uninfected population. An infection can spread within a population only if $R_0 > 1$. For example, measles is transmitted through the air and is one of the most highly infectious viruses with an R_0 (at the level of people, not cells) between 12 and 18. By contrast, HIV is transmitted via blood or sexual contact and is much less infectious with an R_0 of 2-5, though higher at the level of cells.

Figure 1 shows a simple schematic describing viral biology. A pool of target cells (T) is infected by free virus (V) at a rate proportional to both T and V with the rate constant β. Infected cells (I) shed viruses at a production rate p. Free virus is cleared at the rate c; infected cells are cleared at the rate δ. Infected cells may produce cytokines that cause disease symptoms. Antiviral drugs exert their effects by inhibiting viral production or target cell infection. We can use these parameters to calculate R_0, which is directly proportional to the viral infection rate, viral production rate, and total number of target cells and inversely proportional to the rate of clearance of infected cells and free virus.

This basic viral dynamic framework, with disease-specific extensions, can be used to model many viral infections including hepatitis B and C, HIV, and cytomegalovirus (CMV). And, we can elaborate on this framework to address additional questions: What is the effect of combination treatments? How do drug-resistant viral strains emerge under the selective pressure of treatment? What is the impact of adherence— missed or late doses— on the emergence of resistant viruses? How does the immune system respond to clear the infection? And, for curable infections like HCV, what is the viral load threshold for cure?

Integrating Models of the Key Determinants of Patient Responses to Antiviral Drugs

An integrated approach to performing modeling and simulation can be used to address all of these questions.

On the left of **Figure 2**, prescribed antiviral doses enter an adherence model, and actual doses come out. Next, the PK model translates actual doses to drug concentrations over time for each patient.

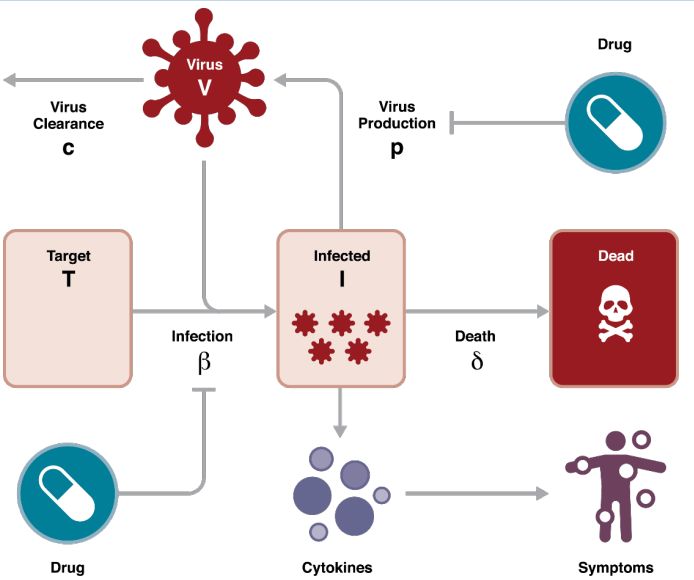


Figure 1

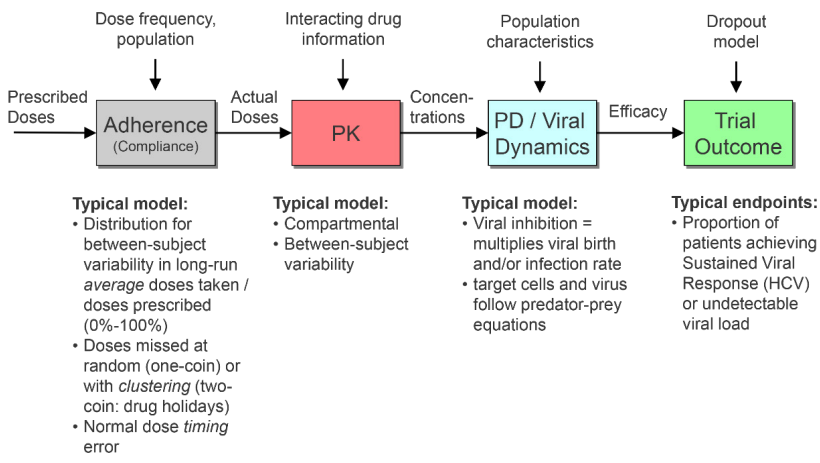


Figure 2

Typically, these are compartmental models with between-subject and within-subject variability. Antiviral drug concentrations then drive viral inhibition and alter viral dynamics. Finally we simulate many virtual patients representing a population to predict the proportion achieving trial endpoints such as a sustained virologic response or undetectable viral load. We can also model the impact of patients dropping out of the study on the probability of trial success. And that could even be modeled together with adherence recognizing that adverse events tend to increase dropouts and decrease adherence.

Modeling Adherence: How does Missing Doses Affect Drug Concentration and Viral Load?

In a perfect world, patients take every prescribed dose on time. Of course, in reality, non-adherence is common and contributes to therapeutic and trial failure. **Figure 3** shows an example of adherence to a drug that's to be taken three times a day. For this patient, the overall adherence is only 53 percent. The missed doses aren't randomly distributed but are sometimes clustered into drug holidays. The figure also shows a double-headed arrow illustrating dose-timing error—when the patient takes their medication, but not at the same time each day.

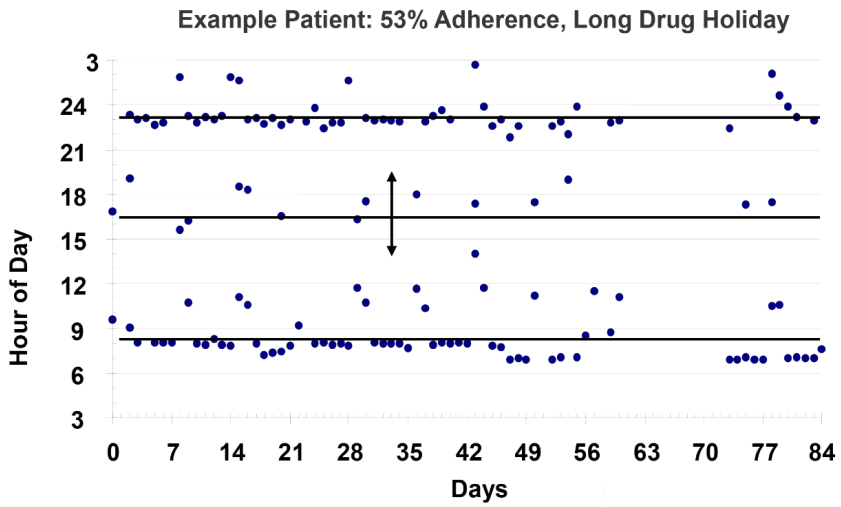


Figure 3

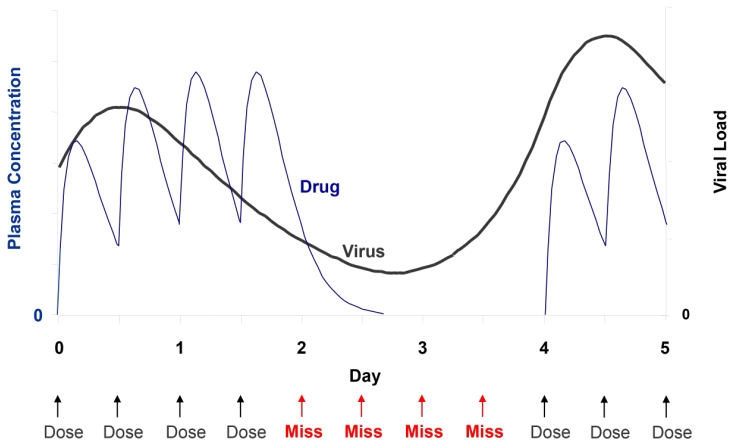


Figure 4

In Trial Simulator, users can assess the impact of both missed doses and dose timing error, which can be set up as a normal or any continuous distribution. Missed doses can be set up to apply to all drugs in the regimen rather than to each drug independently. In addition, users can set up population-level variability in adherence, i.e., some patients consistently take all their doses while others don't.

Figure 4 depicts the effects of missing doses on drug concentrations and viral load. The patient takes the first four doses that leads to increasing plasma drug concentrations and a falling viral titer. Then, the patient's viral load rises after he misses four doses and then starts to recover after he resumes taking the drug.

In summary, basic viral dynamics is similar across many viral diseases. For this reason, users can build viral dynamics models integrated with PK, adherence, and trial design to perform simulations that help assess the impact of each of these factors. Certara's Trial Simulator software is designed to help users build and use these models to support better decision making in antiviral drug development.

Using M&S to Elucidate Drug and Disease Mechanisms

"The FDA has introduced many fundamental advances in how it evaluates drugs for safety and effectiveness, as well as the manner in which clinical trials are guided... So do the introduction of new scientific domains into the development and review process. This includes the more widespread use of modeling and simulation, the greater use of real-world evidence in the pre- and post-market setting, and the adoption of better tools for collecting and evaluating more realtime safety information after products are approved."

– Statement from former FDA Commissioner Scott Gottlieb, MD
on proposed modernization of FDA's drug review office, June 2018

Deeply committed to our mission of bringing new, safer therapies to patients, our scientists work with our clients to advance the discipline of modeling and simulation. That commitment manifests itself across Certara. It is evident in the hundreds of peer-review papers written by our team.

It can also be seen in our integration of mechanistic PBPK and QSP modeling with top down PK/PD approaches. We have incorporated models alongside trials to minimize the impact on clinical volunteers. We have led the industry by developing model-based meta-analysis and clinical outcomes databases to determine comparative effectiveness of new drug candidates and improve competitiveness. And it is evidenced in the hundreds of drug approvals that our modeling and simulation professionals have supported in recent years.

The blogs in this section highlight how we're using M&S helping our clients understand the mechanisms underpinning their investigational drugs and their relevant indications.

Optimizing Immuno-oncology Drug Discovery and Development

Piet van der Graaf | Andrzej Kierzek 07.16.2019

Immuno-oncology – The Breakthrough in Cancer Therapeutics

Cancer immuno-oncology (IO) uses the body's natural defenses to combat cancer. These therapies stimulate an individual's immune system and restore its ability to identify and destroy cancer cells. Anti-cancer immune responses are often inhibited during the spread of cancer. Ultimately, IO therapy expedites long-term responses against cancer by contributing long-lasting memory to the immune system.

Since the 2014 breakthrough approvals for the treatment of advanced melanoma with the IO drugs pembrolizumab (Keytruda®) and nivolumab (Opdivo®), the IO drug market has transformed the oncology therapeutics landscape. These and subsequent IO therapies have delivered long-lasting anti-cancer benefits to patients who previously had few options.

About five years have passed since the introduction of checkpoint inhibitors Keytruda and Opdivo, a fact highlighted at the 2019 American Society of Clinical Oncology (ASCO) conference. Data shared at ASCO showed that nearly one fifth of advanced lung cancer patients treated with Keytruda in an early study of the therapy are alive today, a survival rate quadruple that prior to its introduction. A combination of Opdivo and Yervoy® also significantly improved survival rates in previously treated or untreated metastatic melanoma.

Advances in Cancer Therapeutics Using Checkpoint Inhibitors

There are nearly 3,400 IO therapies in the current global drug development pipeline with 1,300 in clinical studies. Immune checkpoint inhibitors have emerged as a novel IO therapy option for certain cancers. As described by the National Cancer Institute (NCI), "checkpoint inhibitors help keep immune responses in check and prevent T cells from killing cancer cells." According to the NCI, when these proteins are blocked, the "brakes on the immune system are released and T cells are able to kill cancer cells better".

Checkpoint inhibitors, which include programmed cell death-1 (PD-1), PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors, have demonstrated clinical efficacy for a variety of cancers including non–small cell lung cancer, melanoma, urothelial cancer, Hodgkin's and non-Hodgkin's lymphoma, head/neck cancer, subsets of colon and breast cancers, and certain solid tumors.[1]

Checkpoint inhibitors continue to demonstrate extraordinary clinical profiles and extended indications. The development of PD-1 and CTLA-4 inhibitors and other IO agents as monotherapies have advanced cancer treatment. However, while complete regression and higher long-term survival rates is achieved in some patients, only a subset of patients exhibit durable responses.[2]

Developing More Efficacious Combination IO Therapies

Combination therapies using checkpoint inhibitors have been shown to be a viable approach to developing IO therapies with higher responses. While combination therapies are successfully being leveraged, they can also cause higher toxicities. Developing more efficacious checkpoint inhibitor therapies require a better approach to

patient selection through simplified biomarker development and other factors, comprehension of the disease pathophysiology, and optimized clinical trial design. A better comprehension of the multifaceted interaction between a tumor and the immune system will lead to the development of more efficacious treatments.

Second generation IO therapy development focuses on IO therapies that can be synergistically combined with other immunotherapies, or non-IO strategies and emphasizes immunotherapy personalization.[3] Examples include targeted therapies, co-stimulatory mAbs, bifunctional agents, epigenetic modulators, vaccines, nanoparticles, adoptive T-cell therapy, oncolytic viruses, and synthetic gene circuits.

The Challenge of Combination IO Therapy Drug Development

Due to the number of possible drug combinations, coupled with the complex biological and pathological processes involved in IO, developing effective IO combination therapies, particularly in refractory patients, is daunting, complex, and difficult.

Developing successful combinations – involving different modalities and diverse biological pathways – cannot be done randomly. It requires knowledge-based guidance. Further, because the potential number and types of IO combinations cannot possibly be tested clinically, simulation using mechanistic models representing current knowledge is a viable method for combination analysis.

Using a Quantitative Systems Pharmacology Approach to Advance Combination IO Therapy

A Quantitative Systems Pharmacology (QSP) approach for developing combination IO therapies can be used to better predict effective drug combinations. QSP can help correlate the physiological differences between preclinical models and human patients. This approach combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. QSP models are built using human physiology and pathology and provide an *in silico* framework for constructing mechanistic, mathematical models of drug action. QSP focuses on the area between pharmacokinetics/pharmacodynamics (PK/PD) and systems biology. QSP translates PK or exposure into pharmacological effect and builds on insights gained from pharmacometric, PK/PD, and physiologically-based PK (PBPK) approaches with systems biology models of biological and biochemical processes.

QSP is recognized by sponsors and global regulatory agencies as a valuable scientific approach to increase understanding of disease biology, improve target selection, and help to ensure drug safety and efficacy in clinical trials. QSP can also be used to improve the design of First-in-Human (FIH) clinical trials that determine the starting dose and subsequent dose escalations to ensure the best possible protection for human subjects.[4]

QSP is distinct from other Model-informed Drug Development (MIDD) approaches, such as pharmacometrics, since it helps to fill the gaps between the early-stage PK and late-stage drug efficacy using a mechanistic approach. The key to successfully developing IO therapies will be selecting optimal combination therapies and dosing regimens tailored to specific cancers and patient populations. The development of QSP models of interactions between tumor, the immune system, and therapies, combined with the use of The Virtual Twin® technology, will be required for rational development decisions and the regulatory approval process.

Creating an IO QSP Consortium to Tackle IO Combination Drug Development

Certara formed a QSP IO Consortium in 2018 that brings together leading biopharmaceutical companies in a pre-competitive environment to cooperatively develop a robust Immuno-oncology Simulator based on state-of-the art QSP science and methods. The IO Simulator will be used to predict optimal combinations, dose regimens, and biomarkers in computer-generated diverse virtual patient populations. By capturing the complexity of biology, the QSP IO Simulator will enable researchers to explore therapeutic combinations with a virtual population, including drugs that use different modalities. It will help sponsors to answer "what if" questions by providing input and guidance for clinical development. The development of QSP models of interactions between tumor, the immune system, and therapies will be the requirement for rational drug development decisions and facilitating the regulatory approval process.

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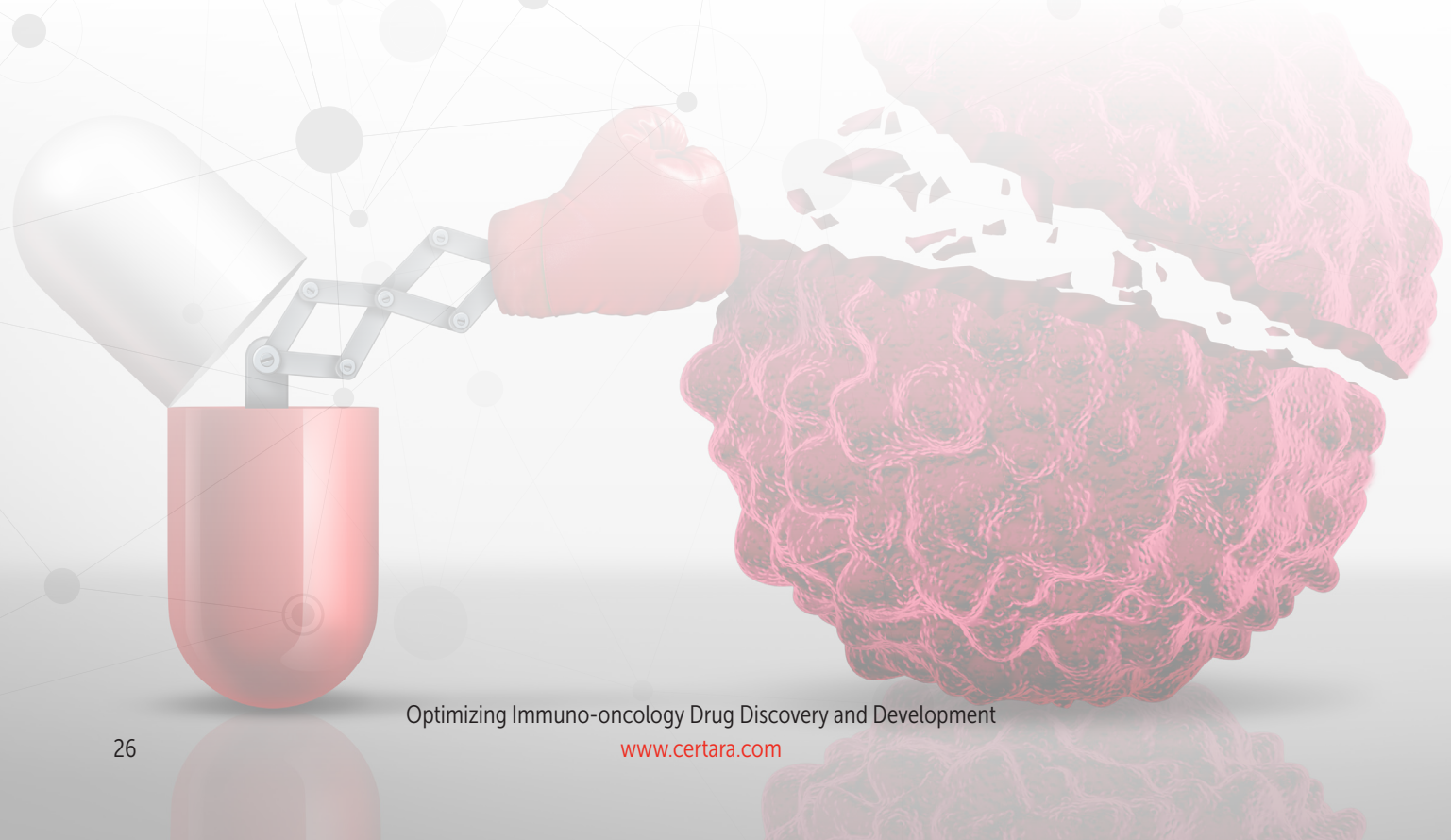

Could Virtual Twin Technology Support Model-informed Precision Dosing?

Thomas Polasek

06.28.2019

Last year, I presented a webinar on Virtual Twin™ Technology that provided an overview of how this technology could be used in healthcare to predict the drug dose for an individual patient that is most likely to improve efficacy and/or lower the risk of toxicity. During the webinar, I provided a general overview of the Virtual Twin concept and demonstrated several applications of the technology for Model-informed Precision Dosing (MIPD).[1] One of the applications described was its use to accurately predict olanzapine (OLZ) exposure in individual patients.[2] The second application was to show how Simcyp-guided ADME biomarker discovery could be used to predict which patients are more likely to experience drug toxicity. Specifically, this was a study with the protein kinase inhibitor dabrafenib, a drug used to treat metastatic melanoma with mutated isoforms of the BRAF gene V600E and V600K.[3]

The webinar generated a great deal of interaction with the participants resulting in some very valuable questions. I hope this Q&A follow-up can help to further elucidate the future role that Virtual Twin could play for MIPD in a clinical setting.

Q: For building the base Virtual Twin model, (1) do you recommend including demographic data such as age, gender, glomerular filtration rate, etc. into account when you compare it to the observed data, and (2) can you talk about the model verification processes such as you would use for PBPK in drug-drug interaction studies?

A: To answer part 1 of the question, yes, you should include as much of that information as possible in the model. We are trying to incorporate all the information that we have about the individual patient. The basic demographic data such as age and weight are all important. So, the more of that information you have, the better. And, if you've got a sense of renal function too, that should be incorporated into the Virtual Twin model. Although you might suspect that some of this is not going to be major for describing between subject variability in pharmacokinetics, I would still include it in the model to try and mimic the actual patient as much as possible.

In regards to your second question on verification, we follow the standard FDA guidance about verification and development of PBPK models. There are many papers now that are beginning to do that. A really nice example is the dabrafenib work that's been done at Flinders University in South Australia. We followed step-by-step the FDA guidance on development of PBPK models – this is the dabrafenib work that I showed during the webinar. So, it's definitely following those standard FDA verification pathways.

Q: Can you speak to some of the challenges or difficulties, and what sort of infrastructure or personnel would be needed to help deploy model-informed precision dosing technology in healthcare settings?

A: The incredible opportunities in this area bring about many challenges. For example, the science of in-vitro, in-vivo extrapolation, a key factor in moving Virtual Twin forward will need a robust and validated way of estimating CYP abundances in the liver and in the gut. Of course, CYP3A is absolutely critical in this regard.

A non-invasive way of getting that information would be fantastic! There's a lot of thinking about marrying top-down with bottom-up modeling approaches and having some structure around that at the moment. For example, how many of the systems parameters need to be estimated

beforehand? In addition, how much do you inform the models after clinical data becomes available? These are critical questions.

If we put the science aside, there are also big challenges faced with the culture of prescribers. In hospital settings and primary care, where the majority of doctors who are doing the bulk of prescribing are not clinical pharmacologists, and they are not focused on precision drug dosing, but rather selecting a dose from the approved dose range which they use all the time. The problem is that these doses don't work for everyone!

During the webinar I mentioned that, in general, I think that between-subject variability and exposure is fairly poorly understood in healthcare. So, there are a lot of educational challenges for individuals, prescribers, and certainly at the junior level, about some basic clinical pharmacology concepts. Basically, they don't realize there's a problem with such variability leading to poor clinical outcomes. If the problem is not known, then there's going to be no impetus for change. Moreover, there will be no recognition of whether these modern, informed, dosing technologies could be utilized. So, there's the scientific challenges and then there's education challenges which we're working on.

In regards to who do we see leading this type of push or who would actually be the end user in applying these technologies in healthcare, it's probably going to be best as a collaborative effort between prescribers and clinical pharmacists. Clinical pharmacy would be essential in driving this technology forward once decisions to prescribe and drug choice has been done by the doctor. The initiation doses and then fine tuning of doses afterward could fall under the clinical pharmacies' area.

Q: Will the clinical study planned for olanzapine use the Virtual Twin technology to decide the dose for individual patients?

A: The Virtual Twin and olanzapine study was a proof of concept study to see if we can predict steady state plasma concentrations in patients. Now that we've done so and we've developed that model, the next phase would be to apply that model and give that information to clinicians to guide dosing. The trouble with olanzapine, which we observed in the Flinders study, is that it's used as part of the acute, agitation protocol. This is why we only had 14 individuals in that small clinical study because it's hard to find individuals who are just starting off olanzapine without having taken it as part of an acute agitation protocol.

A better place to start a clinical impact study would be with clozapine, and that project is currently underway and advancing nicely. Developing the baseline model for clozapine is pretty well advanced, and a clinical study will investigate whether giving psychiatrists that extra information about predicted clozapine exposure could accelerate up-titration during initiations. So, we have our normal initiation protocol for clozapine – half the prescribers will follow that and then half will get the steady state plasma concentration predicted for the individual by the Virtual Twin technology, and then they will be able to personalize the up-titration based on the predictions using their clinical judgment.

So, to answer the original question, we haven't applied the olanzapine model. But, we're certainly looking at applying the clozapine model. And hopefully that should reveal some exciting data in the future.

Q: Are there any conflicts with using patient personal data for making these Virtual Twin simulations?

A: Most of the information is part of electronic health records, basic available information, e.g., age and weight, liver function tests and renal function is – so there's no issue there.

There may be confidentiality issues around when individuals have had their drug metabolizing enzyme or transporter genotyped, how that information becomes available, and how it's utilized. This information around genotyping will need to have a framework for how that information could be applied within the Virtual Twin. And, it's going to be up to the individual to release that information – to populate their

Virtual Twin with that information – if they desire.

Drug-drug interaction information will be obviously transparent because it's going to be part of the patient's e-medication list.

Q: If physicians start to use model-informed precision dosing tools such as Virtual Twin in their clinical practice a lot more, how could they be sure that the Virtual Twin generated by the technology actually matches their patient?

A: This is where we're starting to build the evidence. It's going to be a lot of effort over the next few years going into various areas of clinical medicine to try and establish good quality evidence that is translatable into clinical practice. Initially, it's going to be from an observational point versus an interventional point. You need to build the evidence, as we see with olanzapine, where you are able to get decent predictions of final steady state concentrations focusing on pharmacokinetics initially.

Certara is working with several academic centers who are embracing and developing Virtual Twin technology for several key therapeutic areas to build evidence-based medicine information so that the technology may eventually be available to prescribers more broadly. The goal is that we can scale this to doctors outside of the specialist academic centers and make the technology intuitive and easy for all to use.

Q: What is the applicability of Virtual Twin in the clinic in the context of a new patient regarding the time that's required for the simulations, the analysis, etc.?

A: Initially, it's going to take some time to generate these virtual individuals. You'll need to have a PBPK platform that you can input data prior to patients actually rolling up to clinics. In actuality, you're going to have a Virtual Twin of that individual before they come to clinic already developed because it will take too long to generate them during a consult. But, as time goes by and people become familiar with an established tool, and the evidence builds, that part would become much faster.

But, time is not always a barrier. For example, when a patient is starting a protein kinase inhibitor for their cancer or switching to another one, the time isn't a great factor in that case because the extra resources required for putting together the model for that patient would be absolutely critical for helping select the dose that avoids costly use of clinical resources later on, such as avoiding toxicities. The flip side is, when you're in an acute setting, the time spent developing a virtual twin and the potential benefits of that approach would be much more limited. So, identifying those high impact areas where the extra time that it takes to generate a Virtual Twin is worth it will be important – where the predictions is very valuable in terms of the outcome for that patient. Acute settings, of course not, but chronic, longer-term conditions such as oncology, identifying those high-impact areas of MIPD will be critical.

Subsequent to my webinar, recent publications, scientific interest in, and research into MIPD are growing and gaining momentum. I anticipate that MIPD adoption will follow a similar path to the clinical implementation of pharmacogenomics, which has now become an important consideration in prescribing for some medical conditions and drugs. These recent studies include the application of the "Virtual Twin" approach in the cardiac drug safety arena and identifying patients who could be at higher risk, co-development of companion MIPD tools during drug development to accelerate the generation of evidence required for broader clinical implementation of MIPD, and a report of the first Asian Symposium on Precision Dosing.[4,5,6]

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Leveraging Model-based Meta-analysis to Inform Drug Development Decisions

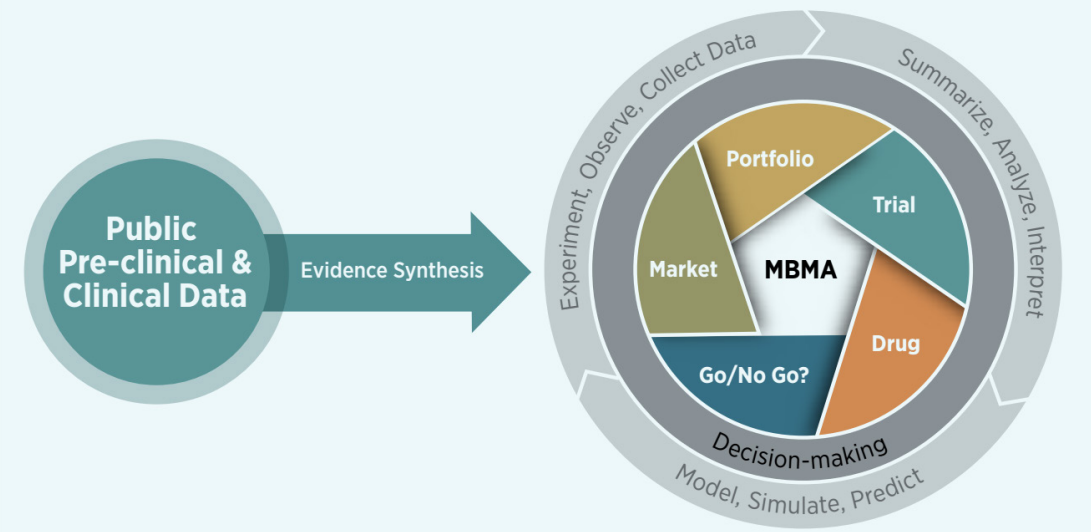
Richard Franzese

11.14.2019

Model-based Meta-analysis (MBMA) is a quantitative framework that uses PK/PD and statistical modeling for leveraging external clinical trial efficacy, tolerability, and safety data to inform drug development decisions. MBMA augments proprietary in-house clinical trial data by systematically searching and tabulating summary results from public sources. These data are then analyzed to characterize the impacts of drug class, drug dose, and time on the response(s) of interest, plus the potential influence of study population characteristics or the trial conduct. Most important, MBMA provides a quantitative understanding of how a new compound may perform relative to the standard of care and other developmental compounds.

How can MBMA Inform Strategic Drug Development Decisions?

The foundation of MBMA lies in leveraging external, summary-level data from independent studies data to inform drug development decisions relating to several key questions. How does our novel compound compare to the standard of care treatments? How do drug classes differ with respect to their safety and efficacy profiles within specific indications? How do various efficacy endpoints



MBMA Can Help Inform Drug Development Decisions

relate to one another? How do trial design and patient characteristics impact clinical outcomes? May we identify sources of variability? May we characterize placebo and treatment effects?

A database based on public clinical and preclinical data, literature, or published trial information may be used to develop a model that can simulate efficacy and other outcomes parameters. When leveraged with drug development learnings, MBMA, through an iterative approach, can help to inform compound portfolio decision making, go/no go decisions, trial/design characteristics, and provide a better understanding of the competitive landscape.

The Advantage of Using MBMA Versus Traditional Meta-Analysis Approaches

Traditional approaches for assessing novel compounds rely on pairwise or network meta-analysis. Pairwise meta-analysis examines interventions or trial arms in pairs. Although this approach is quick and straightforward, it only considers paired intervention-versus-control evidence. Thus, it does not allow indirect comparisons of drugs that have not been compared in a clinical trial. Network meta-analysis combines studies in a network and builds a statistical framework to support indirect comparisons between drugs that may not have been evaluated head-to-head in clinical trials.

The advantage and added value of MBMA – an extension of network meta-analysis – is its incorporation of parametric models for the effect of treatment, time, and patient population characteristics. Thus, MBMA not only compares treatments that have not been studied together in a clinical trial. MBMA may also add pharmacological data such as dose-response relationships and time dependencies, model multiple endpoints, and link biomarkers to clinical endpoints.[1]

How can MBMA Accelerate Clinical Development?

Sponsors use MBMA to inform developing novel drugs for a range of therapeutic areas including musculoskeletal, auto-immune[2], cardiovascular, metabolic diseases, CNS, and pain[3]. Here are a few examples of how MBMA has impacted drug development for indications in these areas.

1. **Osteoporosis**: MBMA was used to run virtual head-to-head trials for comparing denosumab, an approved osteoporosis drug, to drugs in the same competitive landscape. The osteoporosis drug market is crowded with many approved drugs with varying mechanisms of action. Since denosumab had not been compared in clinical trials to other approved osteoporosis treatments, the primary goal of the MBMA study was to compare the time course of biomarkers for measuring the efficacy of osteoporosis drugs – lumbar spine (LS) and total hip (TH) bone mineral density (BMD) changes – during treatment with denosumab or other osteoporosis drugs. Comparing changes in BMD provided insight into the effect of dose, dose frequency, and route of administration. The MBMA used data from 142 clinical trials for preventing or treating postmenopausal osteoporosis. The dose-response relationship for denosumab showed that the approved dosing regimen resulted in maximal BMD changes. The MBMA showed that three years of treatment with denosumab resulted in bigger changes in LS and TH BMD compared to the same treatment duration with competing osteoporosis drugs approved in the US. The MBMA analysis also provided insight into how denosumab compares to other approved osteoporosis drugs without having to spend the time and money on running head-to-head trials.
2. **Psoriasis**: An MBMA study was used to support dose optimization and product positioning of a psoriasis drug. The dose-range for Phase 2 studies of the novel psoriasis drug was selected using Phase 1b data. The Phase 1b data demonstrated a strong proof-of-concept for drug efficacy and all active treatments resulted in a maximal therapeutic effect by the end of the study. The MBMA comparator analysis enabled

proceeding to Phase 2 trials with a dosing range that would include the best likely dose to carry into Phase 3 trials. MBMA has also been used to evaluate other auto-immune disease treatments such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriasis arthritis.[4,5]

3. **Diabetes**: MBMA has also been used to quantify the time course of dose vs body weight for anti-diabetic agents, and to support systems pharmacology model development and glucose clamp trial designs for novel insulins.

Conclusion

MBMA provides valuable information to better understand your compound and the competitive landscape using public preclinical and clinical data with in-house proprietary data. The resulting information makes best use of all available safety, efficacy and market data to inform strategic drug development and positioning.

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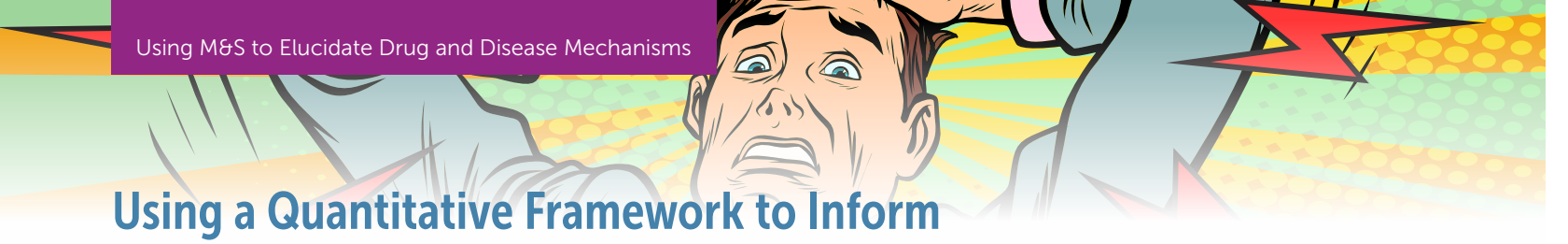


Using a Quantitative Framework to Inform Neuropathic Pain Drug Development

Leticia Arrington 12.19.2019

Model-based Meta-analysis (MBMA) is a quantitative framework that uses pharmacokinetic/pharmacodynamic (PK/PD) and statistical modeling for leveraging external clinical trial efficacy, tolerability, and safety data to inform drug development decisions. MBMA has been used extensively to support developing therapeutic agents for treating a range of diseases including diabetes, autoimmune diseases, osteoporosis, and others.

Last year, we presented our findings at the Population Approach Group in Europe meeting (PAGE) and American Conference on Pharmacometrics (ACOP) on the development of a MBMA comparator model for neuropathic pain (NP). Our goal was to provide a quantitative framework for comparing drugs used to treat diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), and fibromyalgia.

What is Neuropathic Pain?

Neuropathic pain is a disease of the somatosensory nervous system. This chronic pain syndrome affects 7-10% of the population. Pain is characterized as increased activity and dysfunction of peripheral sensory nerves or nerves within the central nervous system and can result from a variety of conditions including cancer, infection, or stroke.

DPN, PNH and Fibromyalgia

Our MBMA studies focused on DPN, PHN and fibromyalgia, three common NP conditions. DPN arises from uncontrolled, high blood sugar levels damaging nerves on the surface of the skin. The extremely painful condition affects approximately 50% of patients with Type II diabetes and can lead to neuropathic ulcers and amputations.

PHN results in burning, gnawing sensations and hypersensitivity of affected areas. It results from viral damage to nerve cells after a shingles infection and mostly occurs in adults over the age of 60.

Fibromyalgia is a common chronic pain condition which affects an estimated 10 million individuals in the US and 3-6% of the world's population. This condition is characterized by widespread musculoskeletal pain, tenderness accompanied by fatigue, sleep, memory, and mood issues. It is usually diagnosed between the ages of 20 to 50 years and is most prevalent in women (75-90% of fibromyalgia patients are women).

All Pain is Not Created Equally

Treatment of chronic, non-cancer pain conditions, such as DPN, PHN, and fibromyalgia, poses a significant challenge. The treatment focuses on improving the patients' quality of life. However, patients respond poorly to opioids or traditional analgesics. NP is treated with medications with varying mechanisms of action, efficacy, and tolerability profiles. Several classes of drugs that have been developed for other indications, e.g. , anti-epileptic drugs and tricyclic anti-depressants, are used to treat NP. Some common medications used include the α2 delta class of anti-epileptics, gabapentin and pregabalin, and duloxetine, a serotonin reuptake inhibitor. With the rise in opioid addiction, physicians use these low-addiction liability classes of drugs before turning to opioids.

All pain is not created equally – different pain mechanisms require different experimental clinical models. Patient factors contribute to the challenge of developing NP drugs. Pain is a subjective experience. Each NP patient has a unique experience depending how their brain processes the quality, intensity, and location of their pain. This will affect patient reported

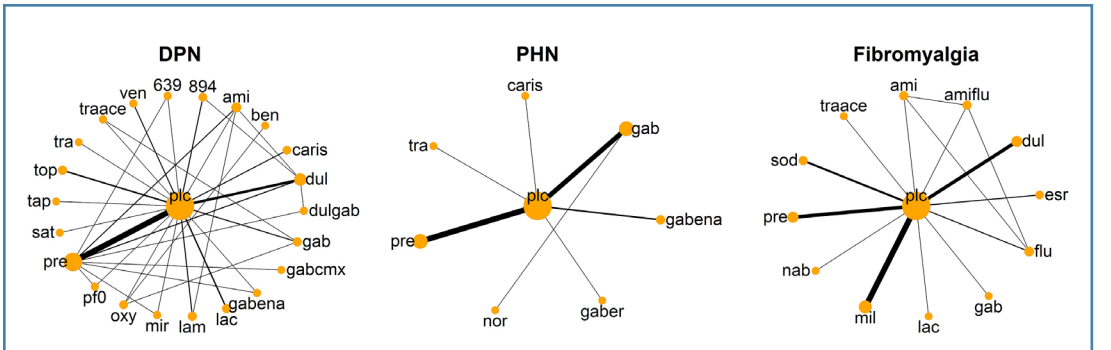
outcomes and contributes to the large placebo effects often observed in NP drug trials.

Trial design also presents a critical challenge for selecting the appropriate methods of evaluating drug-induced reduction of pain intensity– e.g. Visual Analogue Scale, Numerical Rating Scale, etc. Other issues include the lack of active comparators to controls and the impact on efficacy readouts by trial design elements and treatment duration.

Using MBMA to Overcome the Challenges of Neuropathic Pain Drug Development

As a quantitative framework that uses PK/PD and statistical modeling for leveraging external data to inform drug development decisions, MBMA can help chip away at these challenges. We leveraged MBMA in NP to position ourselves for the future, to start gathering data, and to understand the competitive landscape earlier in the development cycle.

MBMA can translate between different measures of pain intensity, pain relief, and responder rates and between short-term and long-term treatment durations. It also allows the opportunity to utilize more data by including trials where treatment effects are evaluated head to head and can leverage indirect comparisons across trials. Important considerations for using MBMA methodology include the type and availability of dose-response, time course information, and covariate distribution data to best inform future inclusion and exclusion criteria, and how to interpret the results.



Network Diagram of DPN, PHN and Fibromyalgia Analysis Datasets

MBMA uses summary level aggregate trial data and fits all data into one model. Data can be leveraged from each indication in the full model. Each node is a drug. Direct comparisons between drugs within a trial are represented by lines. The width of the line is proportional to the number of studies.

Our approach to MBMA for DPN, PHN, and fibromyalgia included the following:

1. The use of Clinical Trial Outcomes Databases focused specifically on these indications. The outcomes databases were developed from a systematic literature review based on predefined inclusion/exclusion criteria,
2. Endpoints of average pain change from baseline, and responder rate for 30% (PID30) and 50% (PID50) reduction in pain, which are the FDA recommendations for measuring NP efficacy, and
3. Age, race, baseline pain score, disease duration, imputation method, trial year, region, and treatment duration were covariates.

MBMA Comparator Model Key Findings

Our MBMA analysis gathered information that can inform developing more effective NP treatments. First, we showed that the placebo response varies across indications – a lower placebo response was seen for fibromyalgia compared to DPN, PHN for the responder rate endpoint. In addition, at label doses the drug effect compared to the placebo response is about half or less, even for approved drugs used specifically for DPN.

We also improved the model by estimating different potency parameters for duloxetine in fibromyalgia and DPN – the average pain model estimated higher duloxetine potency for fibromyalgia versus DPN. These results correlate well with the FDA guidance for duloxetine, which recommends different starting doses for fibromyalgia and DPN.

In the average pain endpoint model, potential covariate effects were identified including mean age, mean disease duration, and mean baseline score. This information will help inform inclusion/exclusion criteria for future trials.

Conclusion

Employing MBMA methodologies can support the future development of novel drugs to treat DPN, PHN, and fibromyalgia in multiple ways:

1. Although there are approved drugs to treat NP, most exhibit small improvements compared to placebo. This presents an opportunity for continued identification of novel treatments and therapies.
2. NP drugs perform differently in different indications, and the placebo effect is different. This will allow us to target particular NP indications with more confidence and increase the probability of success.
3. The order of standard of care can be ranked, and our novel therapies can be compared for efficacy and safety potential. This will inform go/no-go decisions and obtain proof of concepts especially where active comparator arms are not included in this trial design.

In conclusion, MBMA provides valuable information on treatment and placebo effects. Employ MBMA as a tool to better understand your competition and your novel compound.

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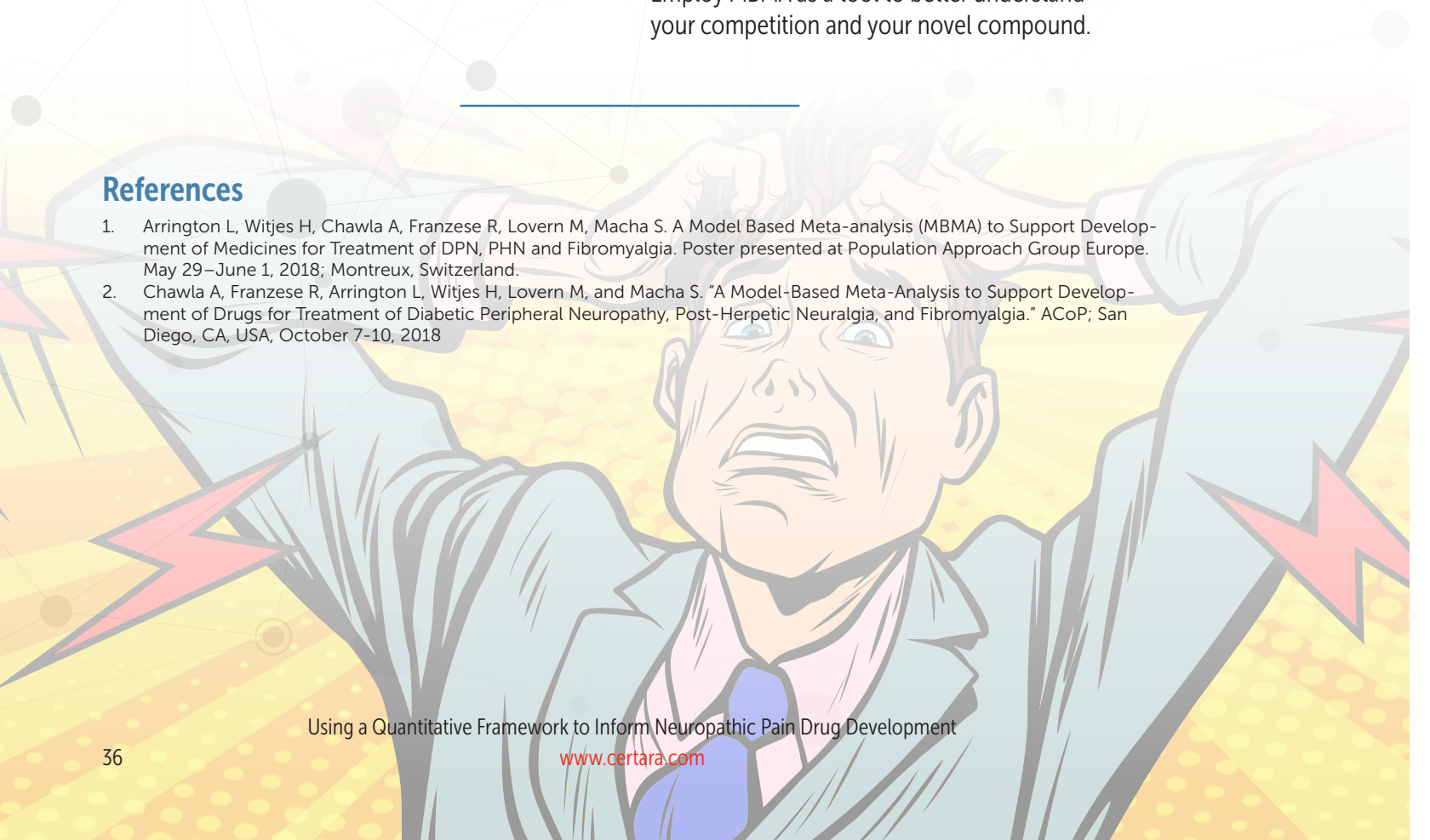

Integrating Organ-on-Chips & In Silico Models for Translational Pharmacology Applications

Christian Maass

09.03.2019

Currently, animal models are the standard for assessing drug toxicity despite their limited ability to predict human toxicity and failure to reduce attrition rates. These models often differ in both morphology and functionality from human organs. Replacing animal studies with more predictive, human-relevant *in vitro* systems could overcome these challenges.

Organ-on-Chip (OoC; also: tissue chips, micro-physiological systems, MPS) technologies are *in vitro* systems comprising biomaterials, tissue constructs, and specialized microenvironments housed in micro-mesofluidic hardware. These systems aim to recapitulate essential human physiology *in vitro* and hold the promise to revolutionize drug development. Potential applications include pharmacokinetics (PK), pharmacodynamics (PD), and safety pharmacology. Both industry partners and regulatory agencies are starting to recognize the potential impact these systems may have on drug testing. OoC has the biggest impact in early drug discovery (high-throughput screening) and pre-clinical studies where they could save up to 25% (~700M USD) of total R&D costs.[1]

To translate results from bench to bedside, academia, industry partners, and regulatory agencies need to collaborate. These partnerships could prove that OoC systems are better predictors of human outcomes than animal models (or simpler *in vitro* models) and establish best practices for using commercially available OoC systems.

A framework that integrates both experimental (OoC) data and computational modelling (quantitative systems pharmacology: QSP/physiologically-based pharmacokinetic: PBPK) approaches can inform first-in-human dosing, establish safe dosing regimens in clinical trials, and identify potential drug failures earlier in the development pipeline thus reducing time, cost, and attrition rates.

Case Studies

Translating Liver-chip Metabolism to Clinical Pharmacokinetics

A recent study[3] investigated population variability in hepatic metabolism of compounds *in vitro* using a liver-on-chip system. First, they employed mechanistic modeling using *in vitro* data to disentangle population-specific clearance of six compounds from the OoC system characteristics. Then, they developed a population PBPK model for one compound (lidocaine) and integrated the intrinsic lidocaine clearance with the virtual population. Using this hybrid in *vitro-in silico* modeling approach, their predicted plasma pharmacokinetics of lidocaine was reasonably close to measurements from a published clinical trial.

Translation of Kidney-chip Injury to Clinical Toxicokinetics (TK)

Another study[4] recapitulated drug-induced nephrotoxicity using a kidney-on-chip system. First, they measured the nephrotoxicity biomarker response over time and for different, clinically relevant drug concentrations. Then, they developed a population PBPK model for one compound, cisplatin. Next, they inter-correlated the *in silico* drug concentrations with the measured *in vitro* biomarker levels and integrated this in a physiologically-based toxicokinetic (PBTK) model to describe the distribution and production of the measured biomarker in a virtual patient population. Lastly, they predicted plasma biomarker kinetics that matched clinically observed biomarkers levels in acute-kidney injury.

Establishing Steady-state Operations of Organ-on-chip Systems

Cell culture media is an essential factor driving tissue functionality. It is therefore essential to use human-physiologically relevant cell culture medium to provide a more accurate microenvironment.

In yet another study,[5] the authors investigated the metabolome of three different OoC systems and determined the tissue-specific nutrient needs of each OoC system. They then demonstrated how this knowledge can inform using OoC systems at more physiological nutrient levels. The authors developed a partial media change protocol for the gut OoC using model-informed experimental design and mechanistic modeling of nutrient consumption. When supplying glucose and removing ~ 15% of cell culture media daily, the system used physiological glucose and lactate levels throughout a 10-day experiment.

Future Perspectives

Integrating OoC and computational modeling approaches will enable translational pharmacology applications that reduce time, cost, and drug attrition rates. Mechanistic modeling of OoC data will improve our understanding of underlying biological principles and inform drug mechanism

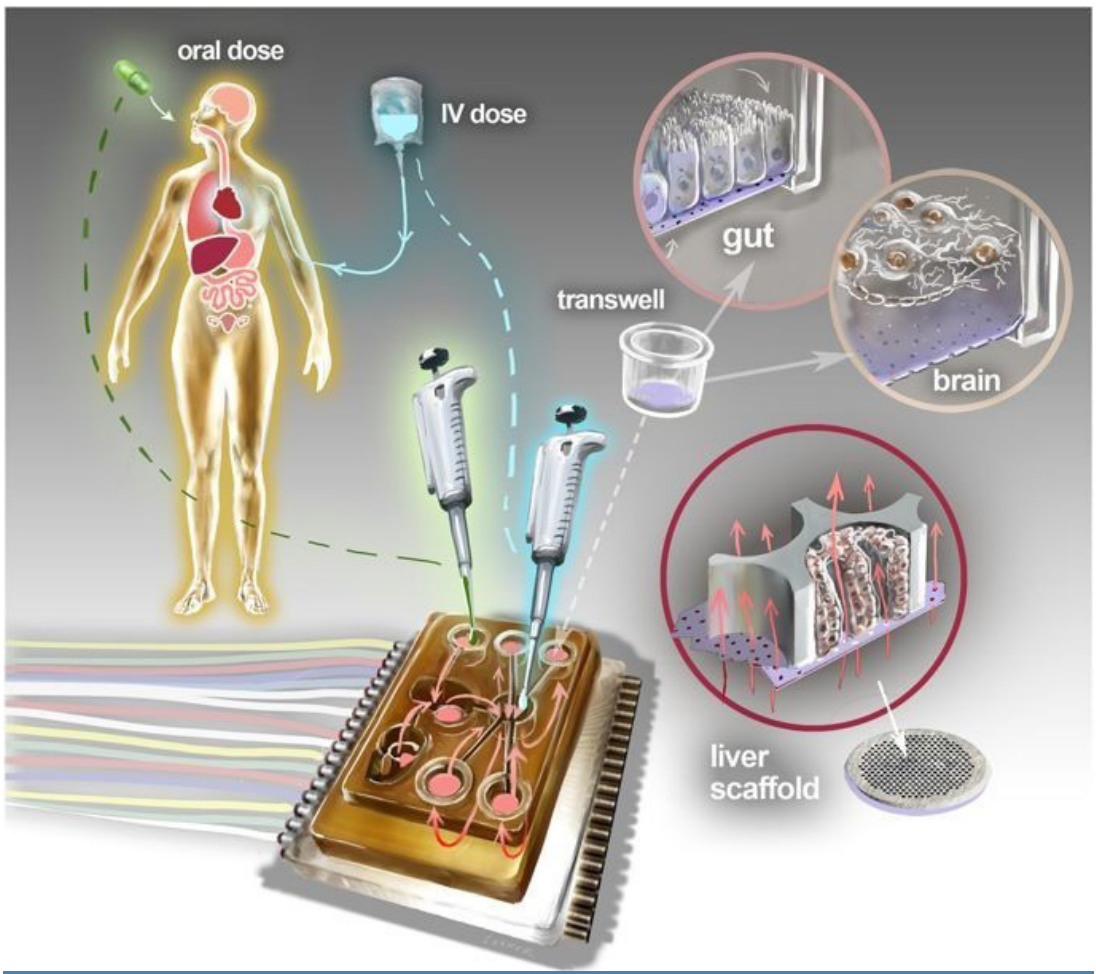

Fig. 1: Schematic overview of organ-on-chip technology. These systems aim at recapitulating size, structure, and functionality of human organs *in vitro*.[2]

of action studies. Single or integrated multi-OoC studies can provide relevant data for pharmacokinetics and toxicology studies *in vitro* already, and integration with PBPK/QSP modeling approaches will translate those results directly to the bedside.

A multi-disciplinary infrastructure and close collaboration and communication between academic and industry partners is needed to realize the predictive power of organ-on-chip systems and computational models.

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Using Simcyp-guided ADME Biomarker Discovery to Prospectively Identify Patients at High Risk of Drug Toxicity

Thomas Polasek 01.25.2019

As novel molecular targets are being continuously discovered and new treatments developed, oncology is one of the biggest therapeutic areas in precision medicine. In particular, new targeted anti-cancer medications that are taken orally, such as the protein kinase inhibitors (KIs), are ideal candidates for model-informed precision dosing (MIPD) technologies.[1] One of these technologies is called physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S). PBPK M&S has been used extensively to evaluate the pharmacokinetics (PK) of oncology drugs for dose selection in clinical trials and to predict the potential clinical relevance of PK drug-drug interactions.[2,3] A significant number of cancer patients taking KIs experience treatment-limiting toxicity, but there is currently no way of prospectively identifying them so that doses can be adjusted. Recently, Certara's PBPK platform, the Simcyp® Simulator, has been investigated as an approach that could predict which patients are more likely to experience drug toxicity.

The protein KIs are a chemically diverse group of drugs used in oncology and hematology. Between patient variability in the PK of KIs is dependent largely on the activities of CYP3A4/5 and P-gp. Indeed, KIs are very sensitive "victims" of PK-DDIs. KIs are traditionally dosed using toxicity guided dosing—the dose is increased until the maximum dose is reached and then scaled back only when adverse effects become intolerable. This approach will insure adequate drug exposure to treat the cancer but is unpleasant for patients. There is growing evidence that PK-guided dosing of KIs to aid achieving steady state concentrations within the therapeutic window (ie, therapeutic drug monitoring) can maintain treatment efficacy and limit toxicities.[4] This evidence means that KIs are also great candidates for MIPD.

Dabrafenib is a good example. Dabrafenib is used to treat metastatic melanoma with mutated isoforms of the BRAF gene, V600E and V600K.[5] Dabrafenib is an inhibitor of the BRAF gene product, B-Raf, which plays an essential role in cell growth regulation. However, dabrafenib resistance typically occurs after about 6 months of monotherapy and cancer progresses. To address this, the FDA recently approved the combination therapy of dabrafenib together with another KI, trametinib, which inhibits mitogen-activated extracellular kinases, MEK1 and 2. Although the combination has survival benefits, about 1/3 of patients experience adverse effects leading to dose reduction and sometimes treatment cessation. A recent study demonstrated that dabrafenib plasma concentrations above 48 ng/ml were associated with higher rates of toxicity.[6]

Simcyp-guided ADME Biomarker Discovery

Recently, investigators at Flinders University in Australia (Dr. Andrew Rowland) explored the idea of using Simcyp to identify the covariates that explain variability in PK.[7] This is called Simcyp-guided ADME biomarker discovery. A full PBPK profile was built for dabrafenib. The FDA guidance was used to perform best practice PBPK M&S.[8] The model was trained against single drug dose studies performed in male healthy volunteers. A univariate logistic regression analysis was used to screen for associations between the physiological and molecular characteristics of *in silico* individuals in the Genentech cancer population and dabrafenib concentration. Multi-variable analysis showed that consideration of baseline weight, body mass index, and CYP2C8, CYP3A4 and P-gp abundance could predict

steady state dabrafenib trough concentrations above 48 ng/ml (ROC AUC 0.94, accuracy 88%).

The next step is to apply the Simcyp model of dabrafenib and the Virtual Twin™ approach to predict which patients are at increased risk of getting toxicities—the exciting part is that this can be done before they commence treatment.

Simcyp-guided ADME biomarker discovery represents a rapid, easy and cost-effective way to identify the major covariates driving between patient variability in PK. Once values for these parameters are known for an individual patient such as their CYP and transporter abundances, MIPD can predict PK for that patient. For drugs with a narrow therapeutic index, such as the KIs used to treat cancer, patients at higher risk of toxicity can be identified and their dose lowered to keep drug exposure within the therapeutic window. This maximizes the benefits of drug treatment for each patient whilst avoiding unnecessary harm from drug-induced toxicities.

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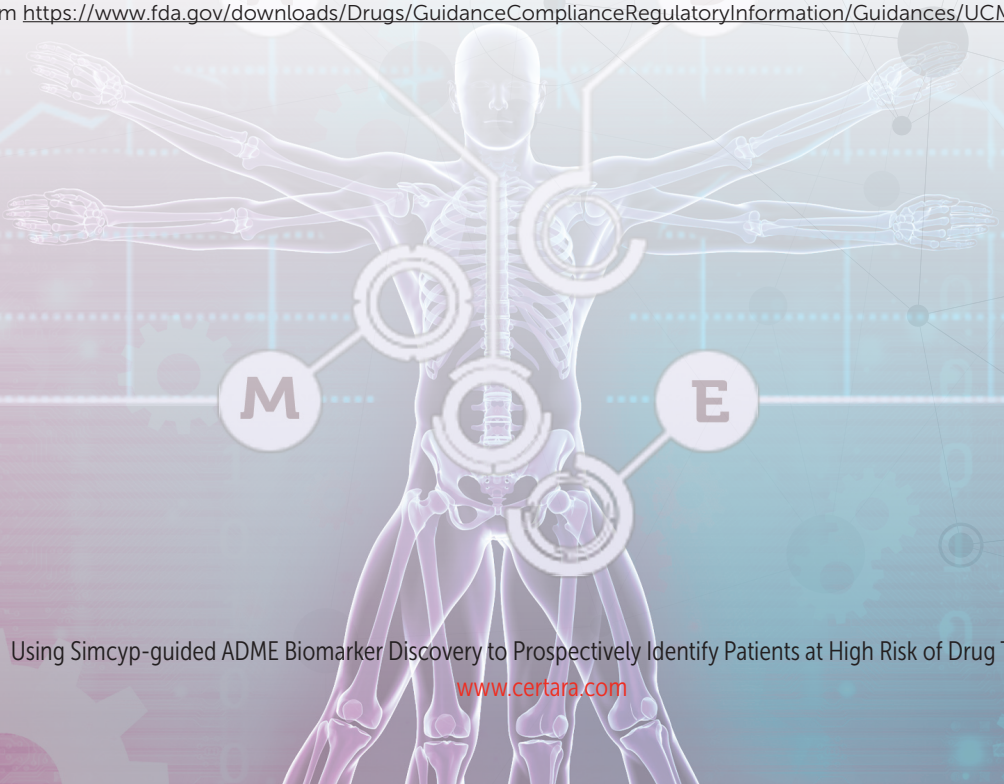

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Crafting Your Drug Development and Regulatory Strategy

Attaining regulatory success is a critical step for any drug program. At Certara, we see regulatory agencies as important strategic partners in our mission to optimize the drug development process. For example, our Simcyp division was awarded two new dermal virtual bioequivalence grants by the FDA to support their Generic Drug User Fee Amendments (GDUFA) priorities of expanding bioequivalence methods for topical dermatological products and improving PBPK models of drug absorption via complex delivery routes. In 2019, this Simcyp PBPK M&S Technology achieved the first and only FDA virtual bioequivalence approval for a 'complex' generic drug.

And we also help support the ability of regulatory agencies to review submissions. In fact, the FDA has renewed its use of Synchrogenix's electronic Common Technical Document (eCTD) review software, GlobalSubmit REVIEW™, providing enterprise-wide use at both FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) divisions. Synchrogenix is our regulatory science division.

Need more proof? In 2019, more than 90% of novel new drug approvals by the FDA were supported by Certara software or services for the fourth consecutive year. Read these blog posts to learn about best practices in charting your drug's development and regulatory strategy.

Building an Early Development Strategy for Complex Biologics

Aaron Moss 09.13.2019

Biologic therapeutics (biologics) are isolated from living organisms whether they be human, animal, or microorganism. Examples of biologics include proteins, nucleic acids, viruses, or cells. Biologics also vary in size and complexity and exert their therapeutic effects through an array of mechanisms. Regardless of their complexity or size, all therapeutics must achieve certain development milestones to ensure the optimal candidates progress while the less optimal do not. The only way that this selection process can occur is through informed decision-making. In this blog, I'll describe some important strategic considerations for successful development of these challenging therapeutics.

The Biologics Roadmap from NME to IND

A few of the primary preclinical development milestones are new molecular entity (NME) declaration, lead selection, meeting with health authorities at the pre- investigational new drug application (IND) phase, and then filing an IND. Meeting these milestones requires answering multiple questions:

- What data are required to move *in vivo* therapeutics through these milestones?
- How are you going to collect that data?
- When do you need that data?

While there isn't a single correct method to carry a complex biologics program through pre-clinical development into first-in-human studies, the necessary considerations will be consistent. These include determining the target product profile (TPP), the starting dose, the dose interval and range, and the optimal biological dose.

What is a TPP?

A TPP is a dynamic resource that serves to guide development decisions across functional areas by creating alignment around a product's attributes and outcomes. It should include plans around the geographies that you plan to seek marketing authorization in (US, Europe, Japan, etc.) as well as the indication and patient population that you want to be approved in the drug label. The TPP should also consider the commercial landscape, and how this new drug will fit into it.

The format of this document varies between organizations, molecules, and therapeutic areas. Be sure to include all relevant information in your TPP. The TPP is a living document and needs to integrate data as it becomes available.

Whoknowz Pharma Ltd			
Target Product Profile – Anti-HCV Assets			
Primary indication	Chronic HCV in adult patients with compensated liver disease; used in combination with current SoC: Peg IFN +/- RBV	**Efficacy**	Naïve: estimate 80% SVR Treatment Experienced: 50% SVR
Clinical Positioning	1st line therapy in naives and treatment experienced patients	**Safety**	No major safety concerns that camot be managed. No significant exacerbation of SoC side effects No significant DDI liabilities
Dosing / Length of therapy	Oral bid/QD **(tid NOT acceptable)** Naïve / Treatment Experienced: ~24 weeks total	**Launch (exclusivity)**	2016(2027)

How to Choose the First-in-human (FIH) Starting Dose

Selecting the FIH starting dose is a difficult aspect of pre-clinical development for several reasons. Complex biologics, especially those that modulate the immune system, can have exaggerated and unexpected pharmacology. Another common challenge is that pre-clinical models often fail to predict the potential for human toxicity or beneficial immune modulation.

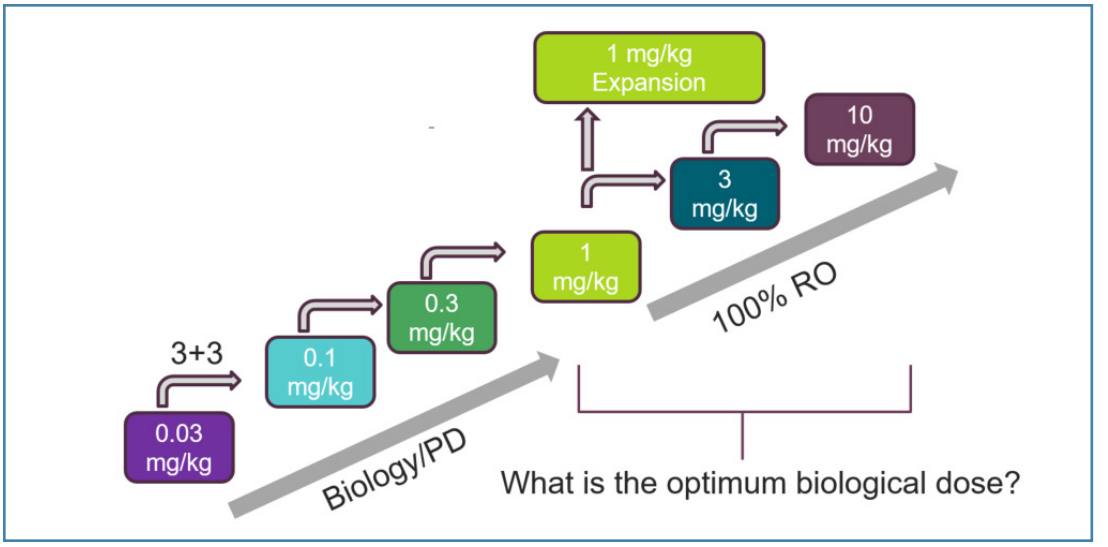
In light of these challenges, how do we provide dosing guidance for molecules with high risk characteristics or minimal translatable data? Start by defining the molecule's level of risk. The risk associated with the safety of a therapeutic will affect the dose level and method by which it is selected. In general, higher risk molecules usually have lower starting doses than lower risk molecules. When you've assessed the level of risk, try to define the dose- or exposure-response relationship using the relevant pharmacodynamic or even toxicology parameters depending on the level of risk.

Dose Selection Methods

Understanding the dose- or exposure-response relationship will help you select an appropriate FIH dose. The dose selection method (minimum anticipated biological effect level- MABEL; minimal pharmacologically active dose- MPAD; no anticipated adverse effect level- NOAEL, among others) you use depends on the molecule's risk. Use more than one method to calculate multiple potential starting doses and be clear about your rationale for choosing these methods.

Biomarkers and Pharmacodynamics (PD)

Often you have to make important clinical development decisions in the absence of clear-cut guidance. Biomarker and PD readouts can inform those decisions, but this is only possible if you ask the right questions during pre-clinical development. If you don't ask the right questions, you risk gathering unclear biomarker or PD data that you don't know what to do with. So, consider what decisions you need to make. What data will inform those decisions? Which specific biomarkers provide that data, and at what point in dose escalation will you observe changes in those biomarkers?



A Robust Clinical Pharmacology Roadmap is Key to Success with Complex Biologics

In summary, biologics are growing in complexity, and many applications are currently in oncology. Key milestones have to be carefully considered in pre-IND early development. These include the TPP, evaluating risk, and selecting a FIH study dose. Attaining these milestones is more complex for complex biologics than for small molecules or simple biologics.

The clinical pharmacology roadmap for complex biologics is centered on the predicted relationship between dose or PK and PD, safety or response in any of the above relationships and also identifying sources of population variability.

Using this roadmap, we can attain marketing authorization and provide new drugs that can help patients.

Benefits of Apocalyptic Clinical Pharmacology During Regulatory Review

Graham Scott

03.08.2019

When developing a drug, pharmaceutical companies need to answer many questions to successfully undergo regulatory review and bring the drug to market. Apocalyptic clinical pharmacology is a framework that drug developers can use to uncover essential relationships between the drug dose and response or outcome. The framework of apocalyptic clinical pharmacology has four different levers that can be adjusted to obtain useful information for the drug development process. Also, pharmaceutical companies have used apocalyptic clinical pharmacology at various stages to help gather information that ultimately helped them decide how to proceed with the drug they were developing. This blog will focus on how apocalyptic clinical pharmacology can benefit drug developers during regulatory review.

Four Important Questions for Regulatory Review

Every drug developer knows that regulatory review can be challenging. Sometimes the process takes much longer than expected. Apocalyptic clinical pharmacology can help drug developers tease apart important information related to the relationships between the drug dose and the eventual outcome. US Food and Drug Administration regulators ask four questions about each New Drug Application (NDA) they receive:

1. Does the clinical pharmacology information list provided in the submission provide pivotal or supporting evidence of effectiveness?
2. Is the dosing regimen appropriate for the general patient?
3. Is an alternative dosing regimen required for subpopulations based on intrinsic factors?
4. Are there clinically relevant food-drug or drug-drug interactions (DDIs) and what is the appropriate management strategy? How is the dose going to be adjusted based on these extrinsic factors?

How Apocalyptic Clinical Pharmacology Helps Answer these Questions

In an earlier blog, I described the four levers that can be adjusted through an apocalyptic clinical pharmacology approach to help drug developers answer the questions that are important for regulatory review. Let's circle back to the levers.

Lever 1: Dose and its Relationship to Response, Pharmacokinetics (PK), and Pharmacodynamics (PD)

For the first question, apocalyptic clinical pharmacology helps uncover the relationships between drug dose and response, which helps drug developers understand how the dose is related to effectiveness (that is what the drug does, and how well it performs in the biological system). Through careful analysis of the relationships of dose to PK, PK to PD, and PD to effectiveness/clinical outcomes, more useful information is uncovered to provide supporting evidence about why a particular dose is chosen and the expected effectiveness (and safety) of the drug at that dose.

Since a key milestone in early clinical development is proof of concept (POC), how can this approach be applied in POC studies which tend to be small and of relatively short duration and in which the clinical outcome is often impossible to assess? A key part of POC studies is the need for clarity on what will be measured, the justification for the measurement in terms of clinical relevance, and what

magnitude of response is likely to be of clinical relevance. The measurement may be a response measurement related to pharmacology or any PD response measurement where the drug developer can be confident that a measurable change in the response is representative of the drug acting as expected. Since the successful POC acts as a stage gate to often substantial further investment in development, the choice of parameters to assess meaningful drug response and the definition of meaningful are of high importance. Thus, thinking about the relationship of the dose and a response that is justified leads to a thoughtful POC study that can inform next steps for drug development.

Lever 2: Frequency of the Dose

Through uncovering the relationships between dose to PK and PK to PD, the drug developer can understand the optimal dosing rate, which includes the dose and how frequently the dose is administered. There are many ways to uncover these relationships using apocalyptic clinical pharmacology and understand how the relationships impact the dosing schedule. In the case studies presented on apocalyptic clinical pharmacology, I discussed the case of needing to optimize the target testosterone concentration in treating prostate cancer. Understanding the interplay between dose, drug exposure, response in terms of desired response as well as safety responses allows patients to derive the maximum benefit that the drug can offer.

Another area of drug development to consider is for large molecules. Most of what I've described so far about apocalyptic clinical pharmacology comes from my small molecule background. But in the case of developing large molecules or even gene therapy, apocalyptic clinical pharmacology still applies and can benefit these development approaches equally well. With large molecules, there is still the need to understand what dose to give and how often to administer that dose. This understanding needs to be supported through understanding the relationships that underpin the dose and response relationship.

Lever 3: Extrinsic Factors and Conditions

Apocalyptic clinical pharmacology can provide insight into how the dose will be adjusted based on extrinsic factors. In the case study on Ibrutinib, DDIs involving the drug's principal route of clearance were substantial. Physiologically based pharmacokinetic (PBPK) modeling enabled the drug developers to provide meaningful prescribing advice on the basis of a relatively limited clinical DDI program.

It seems that PBPK can be used in two different ways for drug development. First, PBPK modeling can reduce the number of studies that are required at the regulatory stage. For example, there might be a co-treatment that is likely to be administered with the drug under development. Then, the simulation in the PBPK model can be done to determine if there is an interaction. Second, during drug development at early stages PBPK modeling can be used to understand DDI risk and then help to streamline the clinical development plan. That is, the apocalyptic clinical pharmacology framework can help avoid doing expensive DDI studies early on in clinical development, and through the use of modeling and simulation a drug developer can predict the DDI risks and then work on decreasing the risk through the understanding gained. For example, if a drug was shown to have a moderate risk of an interaction of about 10-fold increase in exposure (e.g. ~10-fold increase in exposure with an inhibiting co-administered drug), the clinical DDI study may be scheduled earlier in clinical development. However, if the PBPK model indicated a probability of little or no interaction, then DDI studies could be backloaded or avoided completely in the development plan.

With question 4, such approaches provide insights into how to sequence clinical development studies depending on the development stage. These approaches are now well understood by regulatory agencies, and it is up to the ingenuity of the drug developer to apply such approaches to streamline development and provide meaningful labeling for prescribers.

Lever 4: What are Special Considerations for the Populations that the Drug is Given to?

Question 3 is about altering the dose for sub-populations based on intrinsic factors. Let's consider the example of a drug that had highly variable PK. By investigating the relationship of the drug's metabolism to the drug's PK, the drug developer was better able to understand that certain populations metabolized the drug at a different rate than others, and the resulting increased exposure was shown to be relevant to both drug safety and efficacy. Ultimately, an understanding how the dose to exposure relationship is altered in special populations is needed to optimize the safe use of medicines. As mentioned above, describing relationships in models and simulating scenarios allows dose setting and dose adjustment recommendations in such populations.

By applying apocalyptic clinical pharmacology to your drug development program, you can optimize your interactions with regulatory authorities.

Chatting with Mayumi Hasegawa: Global Drug Development Expert

Suzanne Minton 10.31.2019

"Wherever the art of Medicine is loved, there is also a love of Humanity."

– Hippocrates

I cannot think of this quote from Hippocrates, the father of medicine, without also thinking of my Certara colleague, Dr. Mayumi Hasegawa, Senior Director, Integrated Drug Development. She has over 15 years of drug development experience focused on the areas of clinical pharmacology and pharmacometrics. Mayumi specializes in supporting clients in the Asia Pacific regions (APAC; Japan-Korea-Taiwan). So, her love for helping develop innovative medicines that benefit patients is evident. However, in talking to Mayumi, I was also struck by her boundless optimism and passion for helping create a workplace culture of accountability and empowerment. Like Hippocrates, her love for humanity clearly shines. Please enjoy the highlights from our conversation.

Suzanne Minton: How have you found the transition from a senior operational role in pharma to a consulting role in a global consultancy practice?

Mayumi Hasegawa: At Certara, I support clients who are working on Asian-related development programs or submissions to APAC region health authorities. I deliver a wide range of Certara's Model-Informed Drug Development (MIDD) capabilities to Asian customers. I often act like a bridge between regulatory agencies and clients or between Japanese subsidiaries and global headquarters within the client company. Like my previous roles in pharma, my clients expect me to digest scientific data and utilize it for their benefit. My motivation is to convey the benefits of using MIDD approaches both inside and outside of pharma companies.

When I worked in pharma, senior management expected us to educate other departments on the benefits of including pharmacometric strategies in development programs. In addition, I developed strategies for incorporating multiple quantitative

Pictured: Mayumi Hasegawa, Senior Director, Integrated Drug Development

solutions that integrate knowledge and inform decisions. In both my roles in pharma and at Certara, I really enjoy making a difference by providing tailor-made solutions to each project. The key value of MIDD is integrating data from multiple sources to provide a solution that can enhance the efficiency of drug development, both decreasing timelines and cost. In the context of the regulatory approval process, MIDD can enhance the rationale for key development decisions.

In my previous roles at pharma companies, team members made decisions collectively. Whereas as a Certara consultant, I make my recommendations by incorporating public and internal data and the advice of subject matter experts (SMEs) to provide on-time deliverables to clients. Thus at Certara, I keep in mind that my advice to clients should always be professional and well considered because I function like their "drug development concierge."

SM: You have worked in both American (BMS) and Japanese (Takeda) drug development companies. Are there any notable differences in the approach to drug development between American and Japanese companies?

MH: While Takeda is a Japanese company, they have been supporting global drug development programs since the late 1970s. Both companies have been focusing on the US, EU, and Japan as major markets in which to pursue regulatory approvals.

However, my time spent working in the American business environment at BMS gave me some unique insights. American and Japanese business cultures are very different. In the United States, there are many examples of working mothers that hold senior professional leadership roles and share their domestic responsibilities with their partners. During my time working at the BMS Princeton location, I was inspired by their culture of individual ownership of roles where staff works independently while respecting others. After I became the Clin Pharm development head in BMS Japan, I held regular professional development workshops for my team to help empower them to become leaders in their own fields.

SM: What are some major regulatory trends coming out of Japan's Pharmaceuticals and Medical Devices Agency (PMDA)?

MH: In recent years, the PMDA's review process has become as fast the FDA's. Their SAKIGAKE Designation System (introduced in 2015) and Conditional/Time-limited Marketing Authorization System by the Ministry of Health, Labour and Welfare (MHLW) are notable because these systems identify innovative drugs that are initially developed in Japan that show effectiveness against serious and life-threatening diseases. The objective of these systems is to make such drugs available to patients in Japan ahead of the rest of the world. Drugs receive these designations at a comparatively early stage of development and get priority for clinical trial consultation and review.

SM: What do foreign companies get wrong most frequently when seeking marketing authorization for a drug in Japan and vice versa?

MH: I have been involved in numerous interactions with the PMDA, and it is becoming more receptive to innovative approaches by sponsors.

However, the PMDA maintains that it would like sponsors to include Japanese patients in clinical trials before submitting their new drug applications (NDAs). Even though the PMDA accepts model-based approaches, especially in rare disease areas and pediatric indications, it always focuses on a drug's efficacy/safety/pharmacokinetic (PK) profile in Japanese patients. Therefore, if foreign companies ignore this point, their interactions with the PMDA will be negatively affected.

SM: The PMDA sees the next key development in drug development science as "Rational Medicine," which means employing evidence-based medicine to deliver personalized medicines to patients. How can Certara help Japanese companies to realize this important objective?

MH: Since Certara has the ability to use MIDD in every phase of drug development with pre-clinical experts, pharmacometricians, clinical pharmacologists, and regulatory writers, we are already providing cutting-edge solutions to clients and supporting the approval of innovative medicines. Modeling approaches such as physiologically-based pharmacokinetic modeling (PBPK), population pharmacokinetics, exposure-response modeling, quantitative systems pharmacology (QSP), and model-based meta-analysis (MBMA) are all powerful approaches Certara is implementing for clients' projects.

In addition, we often need to use large complex datasets and data beyond what clinical trials can provide to understand drug and disease mechanisms. With this in mind, Certara's diverse team also includes real world data (RWD) and scientific informatics experts. Having a team with these varied skill sets gives clients more options to solve unprecedented drug development challenges.

SM: Can you compare the adoption of model-informed drug development technology in the US vs Japan?

MH: The PMDA has recently embraced modeling and simulation approaches. Sometimes, individual guidances in Japan are tricky, and we must pay attention to them in addition to global guidances such as the International Conference on Harmonization (ICH) guidance. And, there are small differences between the FDA and PMDA which need to be accounted for when submitting an application. For example, in study design optimization, MIDD is used to justify a single-dose study in small or difficult-to-recruit patient populations and to inform label recommendations on the optimal dosing regimen. In silico models can also help bridge clinical data to new populations (pediatric, elderly, etc.) and inform label expansions accordingly.

SM: What made you choose to come work at Certara?

MH: I'm passionate about pushing the regulatory science forward. When I worked in the Expert Working Group for ICH E11A (Pediatric extrapolation), I learned a lot from extensive discussions with global regulators and industry SMEs to harmonize the global guidance. Certara was an attractive opportunity because it offered the ability to help pharma clients who struggle with the methodologies and strategies required to employ MIDD. I really like working with Certara's talented consultants, and I'm excited to bring their skills into drug development programs in Japan.

SM: What advice would you give to a clinical pharmacologist or pharmacometrician just starting out in her career?

MH: Because clinical pharmacology and pharmacometrics (CP&P) are very broad disciplines, the journey to become an expert looks super-long and challenging. But, these subjects are worth your passion! Where there is a will, there is a way. Enjoy all the aspects of clinical pharmacology and pharmacometrics: modeling and simulation, data handling, clinical study design, and negotiation with regulators. I'm happy to go the extra mile in my work because CP&P has so many challenges to solve. The bigger the challenges I face in a project, the more invaluable experience I will gain from it.

SM: Is there anything else that you'd like us to know about you?

MH: On a personal note, I'm a mother, and I want my children to grow up in a world where they can see the impossible as achievable.

I'm passionate about helping drug developers tackle some of medicine's biggest challenges with hope and optimism. I am working towards a future where innovation leads to cures to our most intractable disease challenges, and where life-threatening diseases are treatable. Scientists tend to regard their research as "just research" and not as a driver for real social change. However, we must change this mindset and encourage scientists to communicate more proactively with external stakeholders, potential collaborators, and non-scientists.

In addition, young entrepreneurs using interdisciplinary approaches will be instrumental in solving

our major global health issues. I hope to contribute to more interdisciplinary as well as international drug development collaborations. Cooperation between different scientific communities in various countries is critical to support large-scale research. Scientific diplomacy should include the active participation of not only diplomats, but also researchers, engineers, and business leaders to produce cross-border solutions that will ultimately benefit patients.

It was great to talk to Mayumi, and I agree wholeheartedly with her points about how interdisciplinary approaches are needed to support modern drug development.

RSIDM 2019: Highlights from the 'Ask the Regulators' Sessions

Evan Richardson 02.21.2019

Synchrogenix, a Certara company, was well represented at DIA's Annual Regulatory Submissions, Information, and Document Management (RSIDM) Forum held earlier this month. One of the reasons RSIDM is such a valuable meeting for Regulatory Operations professionals is because it is so well attended by U.S. FDA staff members who participate both as speakers and fellow attendees. We particularly look forward to the "Ask the Regulators" sessions, where FDA representatives answer questions directly from the attendees. Following are highlights from the 'Ask the Regulators' sessions.

Addressed by Multiple Panel Members

- It should come as no surprise that government shutdowns negatively impact work at the FDA. Although application review and product safety activities are generally funded by user fees, most other activities rely on funding from Congress. Work such as guidance creation, standards development, infrastructure updates, and harmonization efforts are all placed on hold during a government shutdown, thus delaying progress.
- A specific form for DMF submissions is currently under development by FDA, with plans for it to be released for use by the end of the calendar year. FDA will post a Federal Register notice before the form goes live.
- FDA currently plans to transition to eCTD v4 (a.k.a., RPS) with a pilot "sometime" in 2020, followed by full acceptance in 2021.
- One attendee sought guidance from the regulators after explaining that some of their clients do not use an eCTD viewer, but instead review eCTD sequences via a web browser. In doing so, they have trouble accessing the style sheets and displaying the XML correctly. The FDA panel unanimously agreed that the best solution would be for the client to use an eCTD viewer to view their sequences.
  - *Do you or your clients needs an eCTD viewer? Our GlobalSubmit WebReview ensures easy anytime, anywhere access to applications.*
- The requirement to include program files with ADaM datasets is specific to each review division. You should consult with your RPM to determine if you should provide them in your application
  - *Synchrogenix recommends that you always provide the program files with ADaM datasets. They should be readily available from your stats vendor, and thus are easy to include in the application with a minimal publishing effort.*

Addressed by Valerie Gooding, Regulatory Information Specialist, FDA

- Gooding confirmed that it is acceptable to submit eCTD sequences out of order and that this practice will not result in a rejection of your submissions. However, she cautioned sponsors to ensure they do not reuse an already-submitted sequence number, as a duplicate sequence number will result in a technical rejection.
- Gooding confirmed that it is acceptable to designate certain blocks of sequence numbers (e.g., the 5,000's) for OPDP or safety submissions.
  - *Synchrogenix regularly employs this practice for our clients, especially for those with frequent OPDP or safety submissions.*
- Gooding explained two important points related to cross application hyperlinking:
  - Such links should be created via the XML backbone

  - Sponsors are encouraged to consider the use of cross application hyperlinks to first do a test submission with FDA before employing such links in a real submission
- Gooding discussed the situation where document A is replaced (v2) and thus hyperlinks within document B now point to the old version of document A (v1). In such a case, she stated that FDA does not expect Sponsors to update document B solely to refresh the hyperlinks from document A v1 to document A v2. She noted that the eCTD viewer clearly identifies for reviewers when such a document has been replaced and they are able to navigate themselves to the current version.
- Gooding (re)confirmed that the Append operator should be avoided in favor of the Replace operator.

Addressed by Mark Gray, Senior Project Manager, CBER – FDA

- Gray was asked if CBER would consider issuing pre-assigned application numbers farther in advance than their current practice. He did not have an answer, but promised to investigate the issue. He noted that CBER had problems with numbers being assigned but never used in the past, which may have led to the current practice.
- There are no current plans to implement eCTD for medical device submissions.
- The FDA is aware that many literature reference PDFs include security features limiting the publishing work that a Sponsor can perform and thus the FDA is forgiving in what they will accept.
- CBER tracks pre-submission correspondence, such as pre-IND meeting correspondence, separately from the IND and assigns them different tracking numbers. When transitioning from pre-submission correspondence to a new IND submission, request a new IND number from CBER (i.e., do not continue using the previously assigned PS number), and begin your IND with sequence 0001.

Addressed by Jonathan Resnick, Project Management Officer, CDER – FDA

- Resnick discussed processing times and delays in receiving CDER's third acknowledgement from the ESG. He revealed that a frequent cause for delays is when the information on your fillable application form (i.e., Form FDA 356h or 1571) does not match the metadata in your application XML (e.g., sequence number, application number, etc.). In those cases, your sequence cannot be automatically processed and must be held for manual processing. If there are no errors present, and your sequence can be automatically processed, the acknowledgements are typically delivered within an hour.
- Approximately 50% of all eCTD sequences received by FDA are using US Regional DTD v3.3. He stated that the FDA would like to see all CTD sequences use v3.3, as it offers many benefits including additional submission types, allows for grouped submissions, and it allows the FDA to use automation to process sequences upon receipt.

Addressed by Suranjan De, Supervisory Health Science, CDER – FDA

- De addressed the forthcoming change to allow the submission of Individual Case Safety Reports (ICSRs) for INDs via the E2B format instead of via eCTD submissions to the IND. In short, the format offers many advantages, including no requirement for cover letters or 1571s, and the avoidance of submitting duplicate ICSRs across multiple INDs. The FDA expects to issue new guidances on this topic by summer 2019 and to begin accepting ICSRs for INDs in the E2B format by Fall 2019. Initially, compliance will be voluntary, but at some point in the future, it will become mandatory.

Additional Sessions Presented by the FDA

Additionally, Ta-Jen Chen, Project Management Officer, CDER – FDA presented a session on the technical rejection criteria for study data. Jonathan Resnick presented a session on eCTD metrics and guidance information.

We learned a lot from FDA staff at this meeting and hope that these tips are helpful to you in developing submissions.

Summary of Health Canada's Public Release of Clinical Information Initiative

Nirpal Virdee

09.16.2019

Health Canada released a guidance on March 12, 2019 pertaining to its Public Release of Clinical Information (PRCI) initiative. Health Canada's objective with this initiative is to make anonymized clinical information in drug submissions and medical device applications publicly available for non-commercial purposes to enable re-analyses of data, foster new research questions, and help Canadians to make more informed decisions regarding their health.

In this blog, I'll also summarize the PRCI guidance, including which past drug submissions and medical device applications for which clinical information may be requested; procedures to prepare information for release; and the implementation schedule for proactive disclosure.

Health Canada Public Release of Clinical Information Guiding Principles

1. All transformation of data should be conducted for the sole purpose of preventing the disclosure of personal information.
2. All data transformations should be accompanied by robust justification, and be applied to limited variables that risk re-identification, not to broad sections of clinical information.
3. Data transformation should favor methods that retain analytical value, e.g. generalization, randomization and offsetting, as opposed to redaction.
4. Must be non-readable text and NOT machine readable or searchable.
5. Ability to submit final redacted documents previously accepted by the EMA through certification
6. Confidential Business Information (CBI) may be rejected if there is inadequate explaining of:
   - how the information was not used to support the conditions of use or purpose for the drug or device, as set out in the submission or application
   - how the proposed information describes a test, method, or assay that is used exclusively by the manufacturer

Observations in the First Submissions Requested by Health Canada

- Process Initiation Meeting (PIM) within 20 days scope of the request and to address any questions by the sponsor
- PRCI email from Health Canada will differ if the request is a retrospective request
- Members of the public may request clinical information from past submissions through Health Canada's clinical information portal with an electronic request form identifying the product name and the information requested (e.g. clinical study report, clinical overview, clinical summary)
- Retrospective requests have no limit on how far back they can go but Health Canada will scan old submission documents for sponsors to anonymize
- EMA formatting and overlay is accepted by Health Canada but terminology differences must be specified in the anonymization report
- Redaction as an anonymization technique is accepted but requires a justification in the anonymization report

On-Request Release of Clinical Information in Past Drug Submissions and Medical Device Applications

Effective March 20, 2019, clinical information from the following past drug submissions and medical device applications may be requested through Health Canada's clinical information portal:

- New Drug Submissions (NDS)
- Supplemental New Drug Submissions (SNDS)
- Abbreviated New Drug Submissions (ANDS)
- Supplemental Abbreviated New Drug Submissions (SANDS)
- Extraordinary Use New Drug Submissions (EUNDS)
- Supplemental Extraordinary Use New Drug Submissions (SEUNDS)
- Class III – IV Medical Device Applications and Amendments

Procedures for Clinical Information in Drug Submissions and Medical Device Applications

Health Canada aims to upload a final redacted and anonymized clinical information package to its portal within 120 days from initiation of the process.

The publication of clinical information under the PRCI initiative proceeds through five phases:

1. **Initiation**: Prior to the initiation of the publication of clinical information, sponsors may elect to attend a one-on-one process initiation meeting (PIM). Sponsors new to the initiative are encouraged to request a PIM prior to starting the process. See section 4.1 of the guidance for instructions on how to request a PIM.
2. **Submission** of the redaction proposal package must include annotated documents with proposed confidential business information (CBI) redactions and anonymization according to the process outlined in section 5 of the guidance. The process of data anonymization should be detailed in a separate Anonymization report.
3. **Review**: Health Canada will review the justifications for each proposed redaction within the annotated documents. Following review, proposed redactions will be accepted or rejected prior to finalization of the clinical information for public release.
4. **Finalization**: Following review, sponsors must submit a final version of the documents, according to Health Canada instructions found in section 4.6 of the guidance.
5. **Publication**: Final documents will be made publicly available for non-commercial purposes through Health Canada's clinical information portal.

Implementation Schedule for Proactive Disclosure

Health Canada plans to phase-in the proactive release of clinical information in new drug submissions and medical device applications. Proactive publication of this information is expected to be implemented according to the following schedule.

Year 1

- New active substances (NDS-NAS), representing submissions for drugs that are not variations of previously approved medicinal ingredients in Canada
- Supplemental new drug submissions containing confirmatory trials (SNDS-c)
- Rx-switch (full and partial submissions to switch an authorized medicinal ingredient to non-prescription status)

Year 2

- New drug submissions (both NDS-NAS and those not categorized as new active substances.)

Year 3

- Supplemental new drug submissions (SNDS)
- Class IV medical device applications

Year 4

- Abbreviated new drug submissions (ANDS)
- Class III medical device applications

Synchrogenix, a Certara company, provides artificial intelligence technology solutions to help you meet global regulatory transparency and disclosure demands. With our ClinGenuity Redaction Management Service (CRMS), we can identify and redact sensitive information with 99% accuracy.

Our solution provides anonymization and redaction services for redaction and advanced anonymization of Clinical Trial Data in the public domain. It is supported by expert reviewers who also help sponsors author anonymization reports.

We look forward to helping you meet Health Canada and other global transparency and disclosure demands.

Do Rigorous Science, Benefit the Patients & Have Fun: Insights from Certara Expert and Former EMA Regulator Eva Berglund

Suzanne Minton 07.31.2019

Drug development is a global enterprise. One of the great things about working at Certara is the ability to learn from fantastic colleagues living around the world.

My Swedish colleague, Dr. Eva Berglund, is a clinical pharmacologist who is now a Senior Director of Regulatory Strategy at Certara after spending a long and distinguished career at the EMA. Eva has also been a member of the Pharmacokinetics Working Party at EMA as well as the former Paediatric Expert Group. She has worked with all types of regulatory applications from marketing applications of new chemical entities – which has been her major focus – to many applications for pediatric indications, new formulations, biosimilars, generics, etc. Her experience also involves the regulatory clinical pharmacology assessment of phase I to III clinical trials including first-in-man studies. Eva is a pharmacist by training and has a doctorate in clinical pharmacology, both from Uppsala University in Sweden.

I recently chatted with Eva about the latest trends in regulatory science, her advice for junior scientists, and what inspired her career change.

Dr. Eva Berglund

Suzanne Minton: Let's start with a fun question: If you could meet any historical figure, either living or dead, who would you choose and why?

Eva Berglund: I would choose Mahatma Gandhi because of his wisdom and endless compassion. I've always been impressed by him. I would probably also need a bit of his patience that he used when effecting change.

SM: You have over 20 years of experience in clinical pharmacology at the European Medicines Agency (EMA) and the Swedish Medical Products Agency. What are you most proud of from your career in the regulatory world?

EB: I'm most proud of the good we did for the patients. Both the guideline work (drug-drug interactions (DDIs), physiologically-based pharmacokinetics (PBPK), pharmacogenomics (PGx), Pediatrics, etc.) and in the day-to-day work with applications. The guideline work improved the regulatory assessments of new medications to align with scientific progress and hopefully, resulted in the better use of medicines in the individual patient.

I'm passionate about pushing the regulatory science forward. I hope that I will continue to do that at Certara.

SM: Can you elaborate on the landscape for pediatric drug development? That's an area of huge unmet medical need as the majority of children's medications are given off label.

EB: The work with the pediatric regulations within the EU was really rewarding because it led to more submissions of pediatric applications and, to some extent, better data being included in those submissions. We have learned a lot in years since the publication of the pediatric regulation. While there's still a lot more work to be done, the approach to pediatric drug development has improved dramatically.

SM: Would you ascribe that improvement in pediatric drug development to the regulations requiring sponsors to conduct clinical studies in children?

EB: Yes, while the pediatric regulations in the EU differ somewhat from those in those in U.S., they both provide a "carrot and a stick" to ensure that pharma companies invest in pediatric drug development. The pediatric PK guideline also explains what kind of clinical pharmacology documentation should be included in a submission and how to extrapolate PK/PD data from adults to children. It always feels good to work in pediatrics where you really feel that you're making a difference. We should be creative and do our very best.

SM: If you had a crystal ball, what regulatory trends would you predict are coming from the EMA?

EB: This spring, the EMA published a strategic reflection until 2025 that includes everything from drug therapies through precision medicine, medical devices, diagnostics, nanotechnology, and developing drugs that have a significant potential to address unmet medical needs. In the strategic plan, one goal was to optimize capabilities in modeling and simulation (M&S) and extrapolation. So, that included both enhancing modeling and simulation and its use across the product life cycle as well as international harmonization of methods via a multi-stakeholder platform. They are also thinking about redesigning how EMA partners work together to enhance knowledge exchange. I would assume that the exchange would be between the Modeling and Simulation Working Party (MSWP) and other groups outside the clinical pharmacology field for example, within Quality or Clinical efficacy and safety.

SM: That's great to hear that the EMA is embracing modeling and simulation. What do American drug developers get wrong most frequently when seeking marketing authorization for drugs in Europe?

EB: From a clinical pharmacology perspective, the most common mistake is to align a submission to FDA guidelines and refer to them inside the EMA application. Scientifically, the agencies have very similar scientific understanding and concerns. We have frequent guideline discussions with the FDA, and we are usually on the same page.

But, there are small differences between the FDA and EMA which need to be accounted for when submitting an application. Some of these

differences relate to choosing a somewhat different approach to solve a certain problem. In particular, how one should address the inevitable gaps in the available scientific knowledge.

Some of the other differences between agencies are consequences of how they are organized. In Europe, assessment of submissions is made by a network of national agencies, not by one large single agency as in the U.S. This difference has both advantages and disadvantages. From the European perspective, the EMA sometimes needs to unify internally and communicate our perspectives both internally and externally. A consequence of this can be seen in the EU PBPK guideline, which discusses qualification of PBPK software for a certain intended use as a way of establishing and communicating the regulatory confidence in a certain kind of simulation.

SM: Can you compare adoption of modeling and simulation in the U.S. versus the EU?

EB: Nowadays, there's little difference between the two regions regarding adoption of modeling and simulation. But, the agencies work quite differently in practice. The FDA performs a lot of pharmacometric analysis. But, in Europe, that is rare due to time and resource constraints. So, EMA regulators may ask sponsors to perform different kinds of analysis or create different plots. The EMA MSWP has gathered pharmacometric assessors from the different member states and is working towards a harmonized viewpoint as well as with assessment of central scientific advice. There has been a big effort in the EU to gain momentum when it comes to pharmacometrics. In Sweden, we have had many excellent pharmacometricians over the years that have pushed modeling and simulation forward.

SM: What attracted you to work at Certara?

EB: Certara was my first choice for its focus on clinical pharmacology. I was also attracted to the ability to work with big and small pharmaceutical and biotech companies over the world while still being able to live in Sweden. In addition, people at Certara are progressive thinkers who have a very high level of scientific expertise. I place great value on these two qualities.

SM: We're glad to have you! The next question relates to mentoring. If you were working with an early career clinical pharmacologist, what advice that you would give that person?

EB: My advice would be to have fun. [Laughs] For me, it's never been about "having a career." My focus has been on implementing innovative science and doing the best for the patients. An additional piece of advice would be to find work that really engages you.

SM: Is there anything else that you'd like us to know?

EB: In my personal life, I'm married and have two grown children. For fun, I love exercising, yoga, gardening, and nature.

SM: It sounds like you have a busy but balanced life in Sweden!

EB: Yes, I intend to do that. Being a regulator in Europe, I've worked a lot internationally. And, I really like that because I enjoy getting different scientific and cultural viewpoints. So, I am happy that I can continue to work in a global environment at Certara.

SM: There are always opportunities to learn from your colleagues at Certara. It is a great environment to work in.

EB: Yes, I've been very impressed with my colleagues. It's good to be in an environment that is all about the science, and how we are going to help clients and patients.

Crossing the Fourth Hurdle: Market Access and Reimbursement for Drugs

Simply attaining regulatory approval is no longer enough for a new drug or health technology to be successful. The pressure is increasing for biopharmaceutical and medtech companies to clearly demonstrate the value of their therapies or technologies in terms of cost savings and improved patient quality of life compared with other available options. Certara partners with global clients to help them effectively demonstrate and communicate that real-world value. We also work with payers to identify equitable payment strategies to ensure that patients can gain access to the best treatments, leveraging our Compass Expert Panel™ comprised of vetted decision makers from health plans, pharmacy benefit managers, care delivery systems, specialty societies, and government organizations.

Certara's Evidence & Access group leverages global population health intelligence to generate the highest level of scientific evidence of the real-world value of medicines and health technologies.

These blogs will feature our thought leaders' insights on market access and value strategies, decision analytics and modeling, real-world evidence solutions, and innovative contracts.

Trends for Market Access, HEOR, and Real World Evidence

Oliver Leatham 05.10.2019

Achieving regulatory approval alone no longer determines a drug's or therapy's commercial success or even guarantees its market launch. Today, each product must be evaluated from a value perspective by payers and health authorities to be placed on the formulary, factored into reimbursement rates, and put into treatment plans before it is available for healthcare providers to prescribe. In this blog, I'll discuss recent trends for using health economics and outcomes research (HEOR) and real-world evidence (RWE) to evaluate the value of medicines and health technologies.

RWE will be Increasingly Used to Fast Track Drug Approvals

In 2016, the 21st Century Cures Act was signed into law. One of its mandates was for the US FDA to develop a framework to evaluate how data from sources other than clinical trials can be used to support drug approvals. RWE is increasingly being used to fast track drug products especially in rare diseases. Thus, a drug may be able to gain marketing authorization on the strength of phase 2b results instead of having to wait until phase 3 clinical trials are completed. Therefore, sponsors won't have to conduct huge and hugely expensive late stage clinical trials. They can collect real world data to show that the drug works just as well in our daily lives as it does in trials. In addition, this approach means that patients receive critical medications sooner and more cost-effectively.

Using RWE to Support Indication Expansion

In addition to using RWE to fast track drug approvals, it will also be leveraged for indication expansion: a regulatory approval for a drug for an indication other than what it was originally approved for. Typically, pharma companies achieve this by conducting additional clinical trials that demonstrate efficacy in the new indication. But, conducting additional studies is both expensive and time consuming, not to mention operationally challenging for very rare diseases.

Another strategy is to first secure marketing authorization in one indication, either the highest price indication, or the one with the highest unmet need (these are often the same). Then expand to patients with other targeted indications using real world data. This approach allows companies to reduce the required number of large phase 3 clinical trials, which is hugely cost saving.

By capturing real world data, you get a better sense of the experience the patients are having on a medication. This allows assessment of the actual medication compliance as opposed to the compliance observed in a carefully controlled clinical study. Thus, the drug company gets a much better understanding of the likely response and patient outcomes under typical conditions.

Technology is Making Drug Development Become More Patient-Centric

Sometimes what's important to patients is different than what we imagine their priorities to be. There's a trend towards making drug products and medical technologies more patient-centric. One way to do this is capturing the patients' feedback. So, patients are being increasingly asked to use smart devices to assess quality outcome measures (QOMs): when they take their medicine, how they're responding to medicines, etc.

In addition, pharma companies are involving patients earlier in the drug development process to

understand how they are managing their diseases, particularly for rare disease patients. For example, imagine a hemophilia patient who has inject herself with medication every day. Maybe she has to spend a lot of time each day finding a vein. Thus, this cumbersome treatment ends up impacting her medical condition as well as her social life. By improving the method and frequency of administration of the drugs that patient uses— perhaps making the medication longer-acting – we can improve her experience.

Capturing the patient's experience is key to demonstrating the 'real' value of your product where it matters the most!

Medication's Value to Society: From "Nice to Have" to "Must Have"

Health care and social care are separate budgets in the majority of health economies. Thus, the impact of medications on society hasn't been a major concern in the past. However, some health systems, such as the U.K., are beginning to combine health and social care budgets. And, it's likely to become more of a factor in the drug approval process in the next decade.

Pharma companies need to consider the patient and social impact of their investigational drug programs. This way, by the time their product hits the market, they've generated the evidence for a cost-effectiveness story around health and value to society. Does your drug help patients maximize the time at school or work? Does it decrease the burden on care givers?

Consider as an example a new drug for chronic obstructive pulmonary disease (COPD) that's not differentiated from the competition. What if its manufacturer provided a system where patients can get advice online or by phone and receive reminders about when to take their meds? This value-adding system might be the differentiator that convinces the health system to reimburse this new product rather than a competitor.

Health Technologies are Leveraged to Tackle the Problem of Medication Non-adherence

Medication non-adherence has been estimated to cost the US healthcare system between $100-300 billion annually.[1,2] Improving medication adherence saves health systems money and supports better patient outcomes in many disease states. Health technologies are increasingly being used to help patients take their medications. For instance, the patient can record on a phone or a device every time they take their medicine. Health care providers are also using text messages to remind their patients to take their medications.

The result of improved adherence on health outcomes can include fewer doctor visits, as well as a reduction in the need for poly-pharmacy and rescue medicines. And, it supports the commercial success of drug products because improved adherence leads to better outcomes. Getting volunteers in a clinical study to take their medication is relatively easy, but payers want to know that it's going to work the same in the real world.

Innovative Contracting and Risk-Sharing Agreements

Risk-sharing agreements between the pharma industry and governments are becoming increasingly popular. They stipulate that if products don't perform well in the real world, then the pharma company has to pay back some money to that country's health system. So, it's in the company's interest to develop practices that help ensure patient adherence and to capture the real world data to prove this.

In conclusion, by embracing advanced Market Access and HEOR strategies early in product development, drug companies are more likely to achieve regulatory and commercial success while better serving patients in need.

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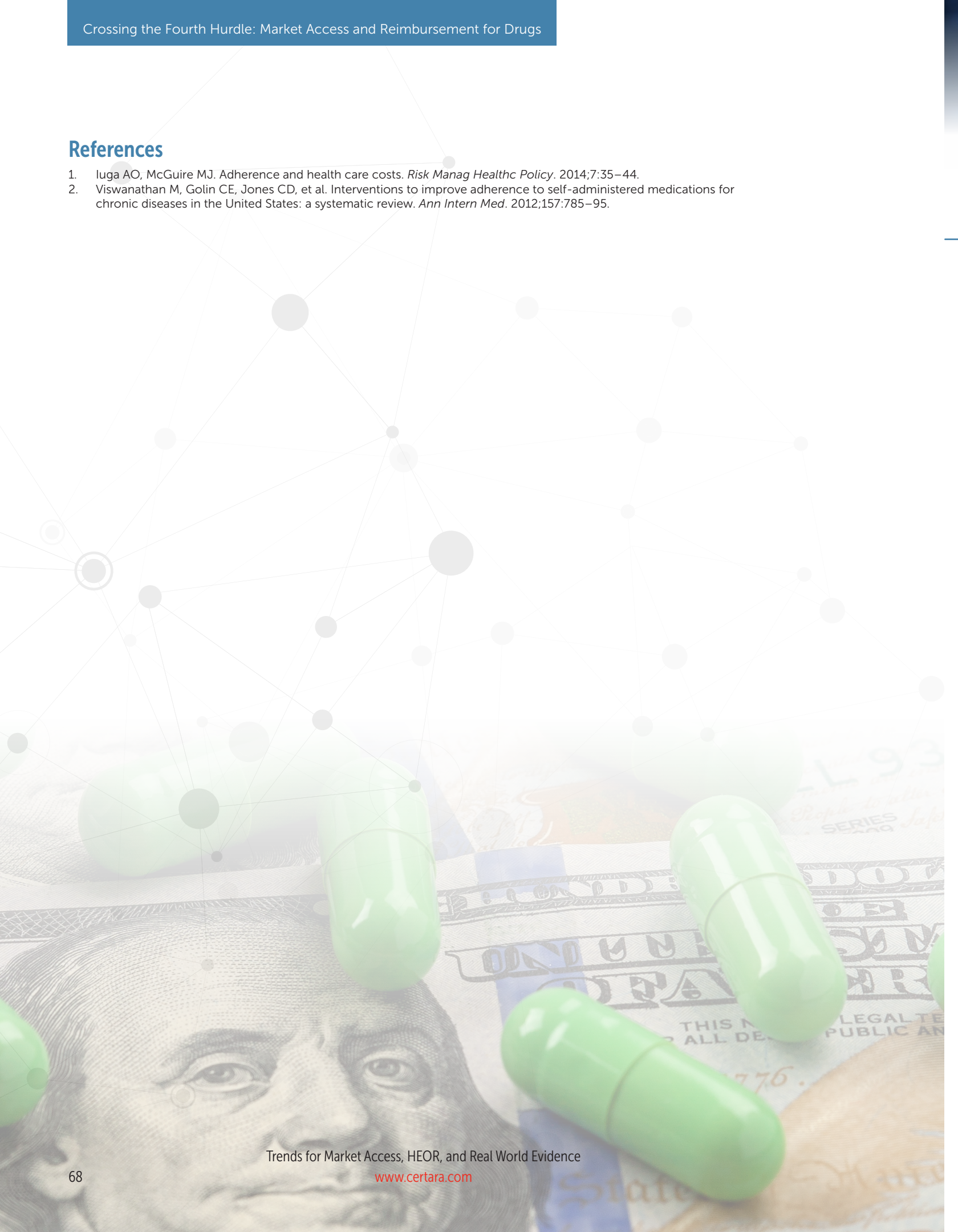


Real World Evidence Marches Forward in Drug Development

Ulrich Neumann

03.20.2019

The end of 2018 ushered in a flurry of new regulatory guidance and sponsor enthusiasm on real-world evidence (RWE) and its adoption in the drug development process. While the collection of real-world data (RWD) and use of RWE is not new, they are now poised to have a profound impact on our industry. Today, it is common practice for regulators to use RWE to monitor post-market safety and to make regulatory decisions. And increasingly, sponsors have been leveraging RWE to support both clinical trial design and observational studies to generate treatment approaches. Likewise, healthcare systems are collecting and using RWE to substantiate coverage decisions.

FDA Publishes its RWE Framework

While clinical trial evidence remains the gold standard for evaluating treatment efficacy, there is increasing interest and potential for leveraging RWD to inform healthcare decision-making. Both the 21st Century Cures Act and the PDUFA VI required the FDA to create a framework for addressing how RWE can be used to better support regulatory decisions. That framework, published at the end of 2018, begins with some key definitions:

- *Real-World Data (RWD)* are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- *Real-World Evidence (RWE)* is the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.
- Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, administrative and medical claims databases) can be used for data collection and, in certain cases, to develop analysis infrastructure to support many types of study designs to develop RWE, including, but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective).

According to Janet Woodcock, MD and Director of FDA CDER, "FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."

Specifically, FDA's RWE Program will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information. The framework will include these considerations:

1. Whether the RWD are fit for use
2. Whether the RWE study design can provide adequate scientific evidence to help answer the regulatory question
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

Pilot projects are underway, and the agency is seeking additional sponsors for such partnerships. This provides a new and exciting opportunity for Pharma and its partners to explore new and innovative ways to use RWE to fast-track products to market; cutting the cost of large phase 3 trials and massively reducing the waiting time for patients to receive life-changing new therapies.

EMA's "Regulatory Science to 2025" Rallies Behind RWE

The EMA just published its 'Strategic Reflection: Regulatory Science to 2025' document. Aligned with the FDA and other global regulators, the EMA views RWE alongside cell-based therapies, genomics-based diagnostics, drug-device combinations, novel clinical trial design, predictive toxicology, modeling & simulation, 'big data,' and artificial intelligence as transformative research endeavors.

To that end, EMA is seeking to:

- create a sustainable, quality assured, flexible framework delivering rapid access to and analysis of representative, longitudinal RWD throughout a product's lifecycle;
- develop a capacity that will enable EMA to rapidly and securely access and analyze large amounts of healthcare data;
- accelerate the implementation of a learning regulatory system based on health economics and outcomes research (HEOR) and other clinical care data;

The agency recognizes the benefit of using RWD to generate complementary evidence across the product life cycle and is committed to promote the use of high quality RWD in decision-making. EMA is further offering consultations in parallel with the European network of health technology assessment bodies (EUnetHTA).

National health systems have long been interested in RWE partnerships. A recent engagement with the French National Authority for Health (Haute Autorité de Santé; HAS) presents a powerful example. The RWE study involved 600+ patients over six centers for a conditional reimbursement scheme in chronic obstructive pulmonary disease (COPD). Over an 18-month timeframe, the therapy was shown to significantly reduce the number of hospitalizations and, therefore, remained fully reimbursed Understanding these opportunities and choosing the right framework for your evidence approach is where expert guidance makes the difference.

Advancing RWE with Certara

In 2018, Certara acquired Analytica Laser, a leading provider of market access and evidence services. Behind the company's quantitative solutions stands an industry-leading team focused on RWE strategies and data analysis for commercial and scientific applications. Driven by the growing value of RWD in generating regulatory-meaningful evidence, experts lead projects to:

- identify opportunities across the clinical development cycle where RWE can answer critical clinical and commercial questions;
- evaluate healthcare technology in the context of public health needs and design RWE study protocols that meet the need of future payers;
- assess and collect relevant data (sources) and aggregate that data in a manner relevant to health systems' requirements;
- perform outcomes research and surveys;
- define patient-reported outcomes;
- conduct burden of illness studies;
- perform retrospective data analysis and natural history patient population studies;
- study relative comparative effectiveness in real-world conditions.

Our teams are proud to be the first successful non-academic applicant to get a positive response towards a research inquiry using the new French health system's 'SNDS' patient database of over 50 million lives. In 2018, we partnered with many industry clients to pioneer accessing and investigating the new SNDS data. Combined with our own ANSER Real World Data Sets and other databases in Europe, this offers a combined population of more than 100 million lives in Europe.

Patient-Reported Outcomes (PROs) as a Benchmark of RWD Excellence

Patient data systematically recorded from routine clinical settings (such as PROs) are one of the key enablers of regulatory acceptance of real-world evidence. However, even strong proponents of drawing on RWD acknowledge that 'the real world' can be messy. The data our research is likely to draw on are often as fragmented, unstructured, and multifaceted as the settings they emerge from. More than ever, experience in closing the so-called efficacy-to-evidence gap is required to formulate evidence strategies in line with the value proposition of novel technologies.

The strong benefits of PROs to the product development strategy rest on high quality scales that can address the target audience's constructs of interest. Our experts help customers choose the most appropriate tools for the research context: health-related quality of life (HRQoL), satisfaction with treatment, adherence, or symptom measures. We can perform cultural adaptations of PROs across different countries, and we design and perform validation studies to assess their psychometric properties (reliability, validity, and sensitivity to change). For cases where disease areas lack robust tools, Certara was able to develop new, reliable ones. We apply Classic Theory, Rasch Model and Item Response Theory in developing and validating PROs. We also have experience in developing Computer Adaptive Test based on IRT.

Certara's Responsibilities as part of the IMI 'Get Real' Initiative

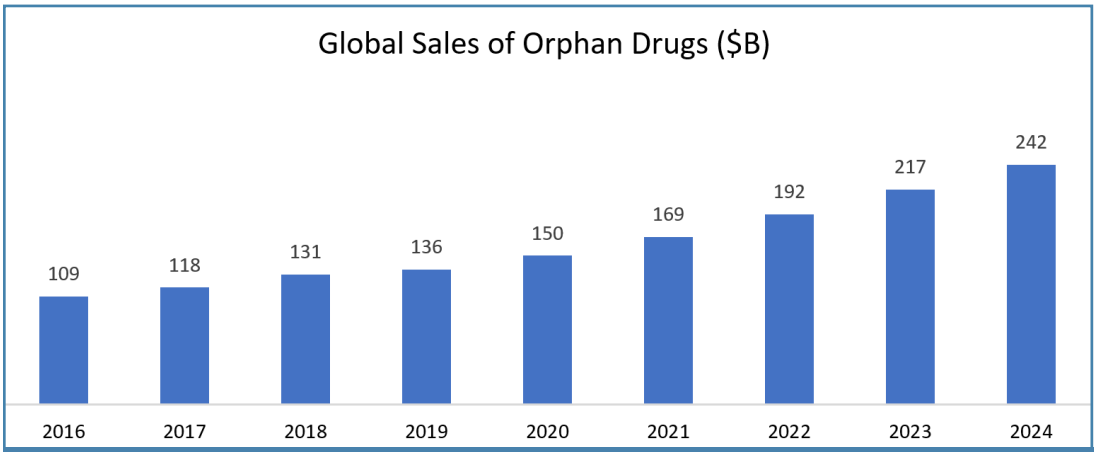
The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership to improve the drug development process. IMI consists of pharmaceutical companies, academia, HTA agencies and regulators (e.g., NICE, HAS, EMA and ZIN). The GetReal Initiative is focused on the adoption of tools, methodologies, and best practices for increasing the quality of RWE generation in medicines development and regulatory/HRA processes across Europe. An active member of this consortium, Certara is specifically involved in the statistical approaches for pragmatic trials and development of best practice recommendations, along with the use of both network meta-analysis (NMA) and multi-criteria decision analysis (MCDA) for assessing the relative effectiveness of drugs.

Rare Diseases: Bridging the Gap between Drug Manufacturers and Payers

Isha Bangia 11.25.2019

The concept of evaluating the value of pharmaceutical products is not new though the changing dynamics of the healthcare system have brought it to center stage. The days of simply determining the market demand as a function of price and choosing the revenue or profit optimizing point are gone. An explicit rationale, also known as the "value-based price", has become a prerequisite for enabling conversations with payers. In this context, the discipline of value demonstration becomes central to the ability to price, and the success of a new technology depends not just on clinical trial-based results and demand based pricing models, but on the explicit determination of value under expected real-world conditions. Payers, including pharmacy benefit managers (PBMs) and managed care entities, are increasingly relying on value-driven tactics to afford and manage therapy costs, especially in the rare disease space.

The EU and US define "rare diseases" differently. In the EU, a rare disease is one that effects fewer than 1 in 200 people. While in the US fewer than 200,000 people are impacted.[1] According to the National Institutes of Health (NIH), there are approximately 7,000 rare diseases, and about 1 in 10 Americans will suffer from one.[2] The Orphan Drug Act (ODA) of 1983 incentivized drug manufacturers to enter these difficult niche markets. Over the years, development activity in this segment has shown no sign of slowing down. In 2018 alone, the FDA approved 35 novel products with an orphan drug designation, the most since the enactment of the ODA.[3] This area is estimated to continue growing and become a $242 billion global market by 2024.[4]



Source: Evaluate Pharma Orphan Drug Report 2019

In 2016, the median orphan drug cost per patient was $83,883.[5] Today therapies can cost upwards of $400,000.[6] Just recently, the most expensive therapy, Zolgensma, was launched at a record price of $2.1 million.[7] As more costly orphan products come to market, payers face increasing pressures to manage these therapies. Rare diseases were once immune to management strategies due to the high unmet need, few, if any, treatment options, and small patient populations. That math, however, has changed. High prices have introduced more uncertainties from the payer perspective around the critical question: Does the medication's value justify its price? These uncertainties have driven payers to utilize different cost containment strategies:

- **Utilization Management**
  Utilization management has been the traditional go-to strategy of payers. Implementing step therapy to ensure initial use of lower cost alternatives, limiting days of medication supplied or prescriber type, and prior authorizations are standard in many different formularies and therapeutic areas. More aggressive management criteria for rare diseases are now being used. Prior authorizations, for example, may now restrict drug use to its clinical trial inclusion/exclusion criteria rather than the FDA-approved label. Renewal processes may require more disease documentation, and orphan products may experience step therapy restrictions in the event of generics or multiple options.
- **Exclusion Formularies and Value Frameworks**
  Rare diseases used to be safe from formulary exclusion lists. However, that changed in 2017 with CVS Caremark's exclusion of drugs for chronic myelogenous leukemia (CML).[8] Since then, others have followed, such as Express Scripts excluding drugs for hemophilia and hereditary angioedema in 2019.[9]

  Payers are also increasingly considering cost-effectiveness models and value frameworks to aid in product coverage assessments. The Institute for Clinical and Economic Review (ICER) is one such organization with its Quality-Adjusted Life Year (QALY)-based cost-effectiveness framework to determine drug value. It has accessed various rare-disease therapies, recommending that US payers do not cover them since their therapeutic value does not justify their pricing within the organization's cost-effectiveness threshold.[10]
- **Evidence Requirements**
  In the rare disease space, manufacturers often rely on surrogate endpoints as a means of FDA-approval. Payers, however, are placing increasing emphasis on real world evidence and long-term outcomes of orphan products outside of submitted surrogate clinical endpoints to determine long-term product value.

The payer perspective is the critical component of optimizing patient access for orphan products. As manufacturers look for ways to succeed in the rare disease space, they must ask: **How can we reduce payer uncertainties around the cost versus value of rare disease therapies?**

From the developer's perspective, key considerations for success in rare diseases with payers include:

- **Value Communication**
  A clear and scalable demonstration of value across all payer archetypes is essential, as rare diseases may not be the top-of-mind indication for payers. Proactive and early engagement on clinical outcomes and health economic modeling can prove beneficial. This effective messaging around value is a key driver of commercial pull-through strategies.
- **Evidence Generation Strategies**
  Rare diseases may see large evidence gaps due to a limited patient size and lack of available information. For similar reasons, evidence generation may also be challenging. Manufacturers must assess evidence gaps and be innovative in generating additional evidence that will convey long-term therapeutic value. Tapping into patient registries, generating data through patient support programs, or collaborating with health systems for electronic medical record (EMR) chart

studies are just a few options for real world data analyses. Predictive modeling and simulation may allow for the translation of clinical trial data to real world outcomes data. Conveying evidence plans to payers may provide further insight into what types of data may be best.

- **Innovative Contracting**
  Manufacturers should consider payers a partner and seek innovative ways to mitigate payer concerns over high price orphan products. Innovative methods for contracting can help decrease payer cost burden while optimizing patient access and care. From risk sharing to annuity models, it is critical to assess key factors such as clinical outcomes, target population, and payer archetype. This can help determine the best contracting strategy to pursue and ultimately reduce access-related challenges.

As rare disease innovation intensifies, developers are turning to experts in scientific value assessment, such as Certara's Evidence & Access team, to bridge the gap between innovators' and payers' perspectives, between value and price, and between profit and sustainable patient access.

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The Expanding Role of Natural History Studies in Drug Development

Sumeet Bakshi | Artak Khachatryan

12.10.2019

Natural history studies follow a group of people over time who have or are at risk of developing a specific disease. This type of study is an important tool in modern drug development and in assessing new health technologies by payers. This is especially true for rare diseases or diseases with high, unmet medical need where thousands of diseases still lack safe and effective treatments, and the populations available for clinical study could be small and heterogeneous.

The term "natural history of disease" theoretically restricts the population to one that has not been exposed to any intervention and where the disease has taken its natural course. However, this patient population rarely exists as some interventions, licensed or otherwise, would have been introduced for the patients at some stage of the disease. Hence, in practice, natural history studies often track patients who have failed earlier treatments and have no further recourse (high, unmet need patients).

Additionally, the regulators and payers are seeking opportunities to maximize the use of real-world evidence in drug development opening a channel for natural history studies. A natural history study can be submitted as a baseline that demonstrates the disease course for untreated patients along with data that charts the disease course of patients given the proposed therapy to show how the natural progression is changed or perhaps halted by the therapy.

FDA's Newly Published Guidance on the Topic

Per the FDA, "Despite a recent wave of medical progress, most rare diseases still have no approved therapies. This presents a significant unmet public health need. One of the challenges we know innovators encounter developing therapies for rare diseases is the lack of natural history data to guide the design of successful clinical trials. Such data comes from observational studies that track how rare diseases develop and progress over time. Sometimes rigorous natural history models can help inform development programs, and even serve as comparator arms for studies where it may be impractical to randomize patients to placebo."

On March 22, 2019, the FDA released its draft guidance, *Rare Diseases, Natural History Studies for Drug Development*.[1] Specifically, this covered the strengths and weaknesses of various types of natural history study designs, common data elements and research plans, and a practical framework for the conduct of a natural history study. It provided considerations for aligning the study design with study objectives and for enhancing the interpretability of study results, patient confidentiality and data protection issues in natural history studies, and potential interactions with the FDA related to these studies.

Per the guidance, there are four key factors to identify when integrating natural history summaries in drug development:

- **Patient population** – Variation in genotype and/or phenotype can affect the characterization, progression, and physiological changes of the disease in sub-groups which is valuable for understanding and developing clinical or other patient studies;
- **Clinical outcome assessments** – Used during trials to assess both safety and efficacy, these assessments include clinic-reported, observer-reported, patient-reported, and performance

outcomes. Natural history summaries can be used to evaluate the ability of a new or existing clinical outcome assessment to detect change or progression in a disease along with performance and reproducibility in the clinical investigation;

- **Development of biomarkers** – A natural history study can be used to develop a biomarker strategy that can be diagnostic of the disease, prognostic of the disease course, predictive of treatment response, or useful in guiding patient selection and dose selection;
- **Use of natural history study data** – Specific guidance on the use of externally-controlled studies. The guidance is detailed on this topic also highlighting the pros and cons of various controls contained in ICH guidance E10. The FDA has previously allowed many drugs to be assessed based on a single arm clinical trial but has also, in absence of a concurrent comparator, encouraged sponsors to design external control arms from patient registries or natural history cohorts. A recent example of this would be Brineura® (cerliponase alfa) for late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease where the sponsor submitted a retrospective comparator no-treatment arm designed from the DEM-CHILD registry.

Contents of a Natural History Study

A *natural history study* is a pre-planned observational study intended to track the course of the disease over time by identifying demographic, genetic, environmental, and other variables that correlate with the disease and outcomes in the absence of treatment. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. Natural history studies can be designed to collect data from case histories or ongoing clinical visits in a cross-sectional or longitudinal manner depending on the desired purpose.

The above guidance identifies two key types of studies:

1. **Retrospective and prospective (longitudinal) natural history studies** – Combining information from patient medical records, scientific literature reviews, and other existing sources of disease-specific information, retrospective studies can help fill critical knowledge gaps and set a course for future analysis. While more robust, prospective studies can greatly inform the development process, but require a longer time investment.

In longitudinal retrospective or prospective studies, data are collected over time, making them more suitable for use as an external control group.

2. **Cross-sectional studies** – Cross-sectional studies collect patient data at a specific time point offering a snapshot of disease at particular time and are relatively cheap and quick to conduct. However, a 'cause and effect' relationship cannot be determined using cross-sectional design.

A mixed design, or hybrid approach combines elements from more than one study design type (e.g. cross-sectional and longitudinal).

Certara's Expertise in Rare Diseases and Natural History Studies

The more we know about how a rare disease progresses, the easier it is to evaluate the effects of investigational treatments and to measure whether a particular treatment changes disease progression or affects patients' longevity or quality of life. Much of the information needed to understand disease progression can be derived from 'natural history' studies.

By supporting optimized drug development, leveraging our unique toolkit of modeling and simulation approaches, achieving global regulatory success, and advising on how to maximize a drug's value and access, Certara has supported more than 100 rare disease drug programs over the past few years. Developing natural history summaries,

performing cross-sectional and longitudinal studies, and advising on clinical trial protocols and selection of patient cohorts is part of our offering.

Rational, modern, and scientifically-based drug development requires understanding the disease pathophysiology. This understanding can be strengthened by natural history summaries.

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ICER's Unsupported Drug Price Increase Report: An Analysis

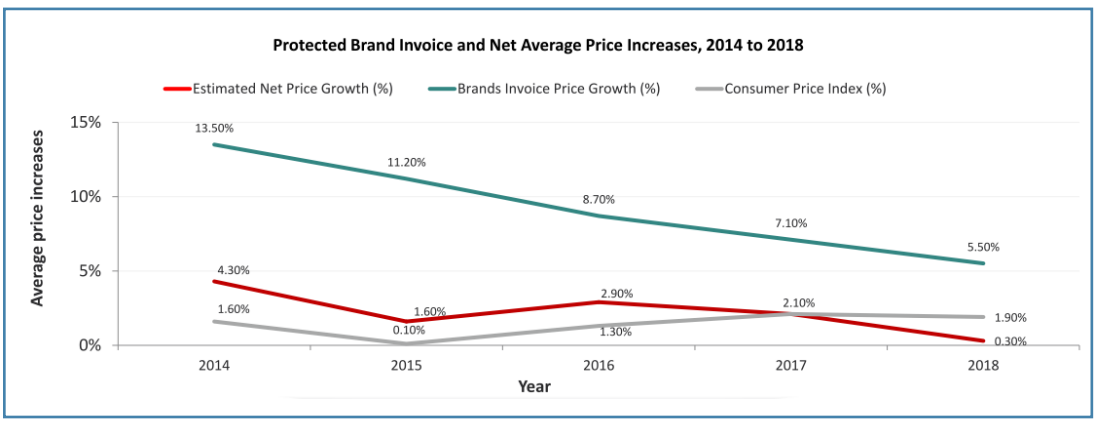
Ulrich Neumann 10.24.2019

Compared to several other developed countries, Americans pay more for worse health care outcomes. A recent *JAMA* study found 20% – 25% of all US health care spending is wasteful.[1] In addition, medical inflation is a massive concern. And, unlike most other developed countries, our current insurance system has patients pay a high price for these excesses. Scott Gottlieb, while still FDA Commissioner, called the status-quo a "Kabuki theatre"[2] where the "sick are subsidizing the healthy." The situation is driving a boom of personal insolvencies due to medical costs.

In this environment, the drug-price watchdog, the Institute for Clinical and Economic Review (ICER), published this month their Report on Unsupported Price Increases.[3] The report picked seven innovative medicines that, in their view, have seen unjustified price hikes. While the study made the headlines, *how sufficient is ICER's analysis?*

Unfortunately, ICER's report is fundamentally flawed. First, selecting seven medicines with price increases as evidence of unsubstantiated price hikes ignores the micro- and macroeconomics of pharmaceutical innovation. Individual companies must price drug successes high to sustain drug development failures. On the macro-level, patents purposefully protect market monopolies in a societal contract where generics enter the market at a fraction of the innovator's cost once brand exclusivity ends. Generally, this societal contract has worked in the US: at least 8 out of 10 of prescriptions filled today are for generics.

Moreover, the report's analysis is problematic. ICER miscalculated the price manufacturers actually realized from the drugs selected for their report. When the researchers found at least a dozen cases yielding a net price above the (gross) list price, or WAC, they removed the list prices for those products. But, they continued with the flawed methodology for all other drugs as if the inability to properly calculate the net prices only pertained to the extreme case where net (somehow) came out higher than gross. Consequently, at least one company disclosed to ICER that net price changes for the assessed products were, in fact, negative. Meaning, the innovator made less money



on the branded medicine than in the prior year. Unfortunately, ICER ignored that correction which would invalidate its methodology. Then, the report proceeded to cite the list price increase, which ICER had misestimated, not the decrease that occurred. Excluding countervailing evidence is unprincipled and violates a crucial research tenet: reproducibility.

But, what happened to list prices? Concerns around drug price inflation have produced data on how much value pharma companies capture. Such research contradicts the ICER narrative and continues to be ignored across their work. Net price increases are estimated to be below medical inflation (data above from IQVIA). Moreover, Express Scripts, one of the nation's largest Pharmacy Benefits Managers (PBM), found that spending on medicines in commercial insurance plans grew just 0.4% in 2018 net of rebates and discounts— the lowest in 25 years. Why does this matter? If list prices climb and net prices stay below inflation, it is the "Kabuki theatre" of reimbursement and rebating that is being subsidized. A win for PBMs perhaps, but neither patients nor drug manufacturers see any gains. And, if pharma applied modest price increases, what happened to the unjustified price hikes ICER claims to have uncovered? Suddenly, the story would become much less egregious.

The ICER report's stated objective was not to evaluate the evidence base, nor to establish what a value-based price for these drugs would be.

"It is important to note that ICER does not have the capacity to perform full economic analyses on the nine therapies evaluated in this report, nor would the time needed to develop full ICER reports (at least eight months) provide information in a useful timeframe for the public and policymakers. Therefore, this report is not intended to determine whether a price increase for a drug is fully justified by new clinical evidence … "- Page ES2

What should we conclude from their analysis then? The report's goal was to determine whether "substantial new evidence existed that could justify [sic]" a price increase. Confused? It's for a good reason! If the report has the limitation of "not being able to determine whether a price increase is justified," it cannot be titled "Report on Unsupported Price Increases." ICER is openly contradicting its own analysis with the stated limitation.

What ICER went on to do is worrisome and matters even more. It asked manufacturers for additional evidence on their drugs. The manufacturers complied with this request only to see ICER selectively ignore dozens of studies and hundreds of literature references that fell into the ICER-chosen assessment window. "Outside of our scope" appears 92 times in the 125-page document. The scope determined the analysis, and it was at best highly restrictive and at worst entirely flawed to answer the research question. ICER admits to discounting many publications, but it's unclear what qualified discounting in the first place. For instance, many studies showed improvements in quality of life benefits and leveraged real-world evidence on the products ICER selected.

Many have demanded the pharmaceutical industry to become more patient-centered. Now that it is, we cannot just dismiss any real-world evidence that runs counter to our hypothesis as "low-quality." To be clear, we can't determine to what degree ICER had done this with the evidence it had received. But, its restrictive approach differs from the FDA which now considers these evidence types as meaningful endpoints, even for approval. And, it differs from payers who want evidence for the real-world patient effectiveness of drugs, not just controlled trial data. ICER further validates the growing concern among patient associations who have long challenged the group on its disinterest in incorporating patient perspectives. ICER dismissed peer-reviewed articles published in scientific journals and posters presented at established conferences. Should ICER unilaterally determine what counts as medical progress across a variety of therapeutic areas? Even when ICER produced its more complete analyses, stakeholder concerns have surfaced. For instance, CVS suggested basing its

formulary on ICER's value assessments in 2018. The resulting backlash from patients and doctors was enormous, and CVS did not proceed with the plan.

We cannot identify obvious research flaws without addressing why ICER is doing this research. In media and many academic circles, ICER orbits as the independent, quasi-governmental agency helping us determine what responsible drug pricing would amount to.

In fact, ICER is overwhelmingly funded by Arnold Ventures. This organization invests heavily in political and research campaigns targeting drug developers for their pricing. Unfortunately, ICER does not focus its health economic analyses on the much larger cost burdens in US healthcare that occur outside of the pharmaceutical benefit. In its report "Unsupported Price Increases," ICER acknowledges that funding from Arnold Ventures enabled the analysis at hand.

We need multiple voices in this debate, including views outside the pharmaceutical industry. But, we also must be aware *who* produces these. ICER is not a public advocate, nor is it mandated to provide objective, academic analyses. Unfortunately, in trying to grab headlines, the recent ICER report picked data points to support a narrative. There is no reason ICER cannot provide one of the perspectives in the debate, and do so with a credible point of view. We may just want to stop elevating that one voice as the 'independent one' in the important discussion of drug pricing.

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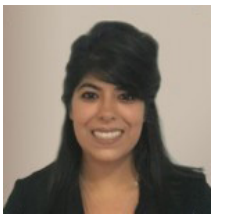
Sumeet Bakshi is VP, Real World Evidences Solutions, in Analytica Laser, Certara's Evidence and Group. Sumeet qualified as a physician from the University of Mumbai (India) and holds an MBA from the Saïd Business School, University of Oxford (UK). Prior to joining Analytica Laser, he had gained multi-disciplinary experience working through roles in sales, brand management and strategic planning in companies such as Pfizer and J&J. Sumeet joined Analytica Laser in 2010 and has developed an extensive expertise in real-world evidence strategies and access throughout Europe. At Analytica Laser, he has set up real world research platforms for complex study programs in many therapy areas and has also consulted for clients on projects in the areas of real-world research, evidence generation strategy, strategic positioning and pricing & reimbursement strategy, amongst others. Sumeet brings strategic thinking, insightful perspectives and strong project/program management skills to the projects that he contributes to. He is a senior member of the decision analytics team.



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Isha Bangia brings a combination of clinical and strategic experience to Certara. She holds a PharmD from Rutgers University and an MBA from Johns Hopkins. Her background as a pharmacist provides clinical perspective into retail and hospital settings where she has been involved in market access and clinical care at the provider level. Isha has also participated in P&T committee meetings for formulary decisions. Prior to joining Certara, Isha was a consultant at Prescient Healthcare Group, focused on competitive landscaping and go-to-market strategies. She has past experience from Zitter Health Insights focused on payer primary and secondary market research to better understand market access barriers (e.g. step therapies and prior authorizations) for manufacturers. She has worked across multiple therapeutic areas including oncology, biosimilars, diabetes, vaccines, and rare diseases.

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Richard Franzese is a consultant at Certara based in Nashville, TN. He has expertise in population PK, PK/PD modeling and simulation, and model-based meta-analysis. Richard holds a master's degree in physics and a doctorate in engineering, both from the University of Oxford. He has therapeutic expertise in infectious disease and cardiovascular disease.

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Andrzej Kierzek graduated with an undergraduate degree in molecular biology from the University of Warsaw and received a PhD in biophysics from Polish Academy of Sciences in 1999. Since 2004, he has been working at University of Surrey, UK and became Professor of Systems Biology in 2011. In April 2016, he moved to Certara QSP as Head of Systems Modeling. He is still a visiting Professor of Systems Biology at Surrey. Andrzej has more than 20 years of experience in computational biology. He has been working in computational systems biology for over 15 years. He published models and software for analysis of molecular network dynamics and constraint-based modeling of genome scale metabolic networks, including metabolic reprogramming in cancer. Currently, his research focus is on immune-oncology and immunogenicity.

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Oliver Leatham is Vice President of Global Value & Access at Analytica Laser, Certara's Evidence and Access Group. Oliver holds a BA Hons and has over 17 years' experience in his field. Formerly Global Head of Pricing & Market Access at PAREXEL, Oliver integrated specialist Teams across a number of functions including Real World Evidence, Late Stage Research, Regulatory, Epidemiology and Commercialization. Prior to this, Oliver was Head of Market Access at Astellas with a Team of 33, made up of data analysts, HTA experts and field market access representatives, who negotiated daily with Payers at National, Regional and Local Levels. Oliver has sat on the AWMSG (Wales HTA), written for Harvard Business Review and chaired multiple EU Market Access Symposia. Oliver specializes in innovative contracting and has been involved in some of the earliest and most successful conditional reimbursement negotiations in Europe to date.

Ellen Leinfuss
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Ellen Leinfuss is responsible for developing the company brand and "go to market" strategy for the company's many technology-based products and consulting solutions. She serves as the key spokesperson for the company. Ms. Leinfuss brings more than 30 years of experience leading marketing, business development, and sales management groups for technical and scientific-based organizations. Prior to joining Certara, she served as SVP and Head of Life Sciences at UL EduNeering, a global provider of regulatory compliance educational solutions, delivered via cloud-based technology. At UL, Leinfuss directed the strategic development of the company's solutions to the life science market, including pharmaceutical, medical device, biologics, clinical, and managed care health plans. In addition, she managed the company's strategic alliances, including the company's 15 year Cooperative Research and Development Agreement (CRADA) with the US FDA. Leinfuss possesses an MBA in marketing from the City University of New York and a BS in chemistry from the State University of New York.

Mark Lovern
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Mark Lovern has 14 years of experience in applying modeling and simulation tools and techniques toward optimally informing drug development decision-making. Mark's previous work history has been split approximately equally between biopharmaceutical companies (GSK and UCB) and companies that support the biopharmaceutical industry (Quintiles and Pharsight). In addition to modeling pharmacokinetic and pharmacodynamic data across a wide variety of compounds and therapeutic areas, Mark has also taught over 50 technical training workshops on modeling tools and methodology. His most recent therapeutic area experience has been with therapies for infectious disease and autoimmune disorders. Mark was awarded a Ph.D. in Biomathematics from the North Carolina State University in 1997. His favorite leisure activities include hosting dinner parties, traveling, reading, and enjoying films.

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Christian Maass is a research scientist in the quantitative systems pharmacology group at Certara. He received his PhD in Medical Physics from Heidelberg University, in 2015. He then completed a 3-year postdoc at the Massachusetts Institute of Technology (MIT), Cambridge, MA, USA, where he focused on application-driven method development for organ-on-chips (OoC) in safety pharmacology. In 2018, he joined Certara's Quantitative Systems Pharmacology (QSP) team. Since then, he has been leading efforts to integrate organ-on-chip (OoC) and computational modeling for translational pharmacology applications.

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Scientific Communications Manager, Certara

Suzanne Minton is the scientific communications manager at Certara. She helps develop the science-focused, value-oriented content that our customers go wild for. Dr. Minton received her doctorate in pharmacology from the University of North Carolina at Chapel Hill School of Medicine. When she's not writing about the hottest problems in drug development, Suzanne enjoys spending time with her husband and two young children.

Aaron Moss

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Aaron Moss joined Certara in November 2017 as Director, Clinical Pharmacology with 10 years' experience in translational modeling and simulation (M&S). Dr. Moss has extensive experience in the pharmaceutical industry where he has held positions at Alpine Immune Sciences, AbbVie, Seattle Genetics, Amgen, and Sonus Pharmaceuticals. He received his PhD in Pharmaceutics from the University of Washington, where his research focused on pharmacokinetics, transporters and drug-drug interactions (DDIs). Throughout his career in pharma, Dr. Moss has used his expertise in quantitative pharmacology to support the progression of lead candidates from discovery and early clinical development through to regulatory IND submission. His recent research has focused on the immuno-oncology and auto-immune therapeutic areas where he developed biomarker strategies, performed PK/TK analysis and reporting, and implemented immuno-oncology translational PKPD, including first-in-human dose and dose regimen projection. Dr. Moss has proficiencies in database build and plug-in development for CADs software such as AutoCAD and Solidworks. For the past 5 years he has shared his expertise with budding clinical pharmacologists as an Affiliate Instructor in the School of Pharmacy, Department of Pharmaceutics, at the University of Washington.

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Edward Nehus is a Pediatric Nephrologist in the Division of Nephrology at the Cincinnati Children's Hospital Medical Center and an Assistant Professor at the University of Cincinnati, Department of Pediatrics. Dr. Nehus conducted and published a cross-sectional study, which investigated the association of serum resistin with cardiovascular risk factors in children with chronic kidney disease. In addition, he recently published a study evaluating the outcomes steroid-avoidance protocols in pediatric kidney transplant recipients. He continues to be the primary investigator for ongoing studies that explore pharmacokinetic alterations in critically ill children receiving continuous renal replacement therapy.

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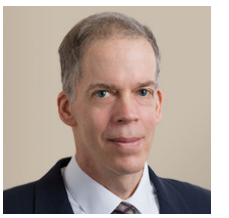
Ulrich Neumann, MSc MA BSc BA, is the head of US Market Access for Certara Evidence & Access, where he leads the company's US Market Access and Commercial Strategy team. With a dual background in business and public administration, he focuses on reimbursement and pricing issues, as well as activities on the political, legislative and regulatory landscape to assess policy drivers, enablers and challenges to market access. His commercial experience lies in defining product strategy, value messaging and b2b brand development. The founder of several ventures, Ulrich has worked on go-to-market projects for 12+ year, leading multimillion dollar P&Ls and cross-functional academic/commercial teams. He published two books in the policy field as well as various pharmaceutical articles, whitepapers, reports and posters around critical managed care topics such as reimbursement of infused vs. oral oncolytics, formulary placement, evidence frameworks, payment reform, outcomes-based contracting or manufacturer IDN collaborations. Ulrich holds an MSc from the London School of Economics, an MA from University of Southern California, Annenberg School and Marshall School of Business. He recently led a seminar at Rutgers Business School (Irvine Center) on clinical trial innovation and is a nominated Fellow of the Royal Society of Arts and Commerce since 2014.



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VP & Lead Scientist, Certara

Bill Poland has provided pharmaceutical companies guidance in drug development decisions through scientific and decision-analytic modeling and simulation since he joined Certara in 1998. In over 40 projects for top pharmaceutical companies, Dr. Poland has advised on trial and program design for HCV, HIV, and other therapeutic areas, using integrated treatment adherence, pharmacokinetic, pharmacodynamic, and trial models. Recommendations included go/no-go, doses and regimens, arm sizes, and target populations. In central nervous system diseases, he has used simulations to develop flexible strategies for optimal Phase 2-3 development of multiple drugs with overlapping indications, incorporating market models to value outcomes. In oncology, he has performed and reported population exposure-efficacy and exposure-tolerability analyses for regulatory submissions. Poland's research interests include practical viral dynamics modeling, portfolio optimization, and Bayesian adaptive program design trading off efficacy and side effects, for which he is co-author of a patent submission. Before joining Certara, he performed decision analyses for pharmaceutical and other industries at Strategic Decisions Group. He received his Ph.D. in Engineering-Economic Systems from Stanford University in 1994. He has an M.S. from the same department, an M.S. in Operations Research from the University of California at Berkeley, and a B.S. in Engineering and Applied Sciences from Harvard University.

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David Salinger is a Director of Consulting Services at Certara Strategic Consulting. He joined Certara in October 2015 after spending seven years at Amgen, where he served as both scientific director, quantitative pharmacology and principal scientist, quantitative pharmacology. Prior to joining the pharmaceutical industry, Dr. Salinger served as a research scientist for population kinetics in the department of bioengineering and the University of Washington. Additionally, he served as a research consultant at Columbia Basin Research, where he was responsible for the development and implementation of algorithms for data analysis, modeling and simulation of salmon migrations. He obtained his PhD at the University of Washington and Masters of Science from Penn State.

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Graham Scott has more than 30 years' experience in the pharmaceutical industry, having worked in various roles in pre-clinical, early clinical, and clinical pharmacology drug development. He has varied and deep experience in early clinical development, having led more than 30 FIM studies and "early-in-human" studies. He has interacted with all major health regulatory authorities, having led and overseen multiple filings. His work experience has been with top 20 pharma companies in the UK, US, and mainland Europe. Most recently, Dr. Scott led Takeda's European clinical pharmacology team and one of their global clinical pharmacology therapeutic areas. He has completed a leadership program at INSEAD, is a member of the Royal Pharmaceutical Society, and obtained a PhD in Drug Metabolism from the University of Strathclyde.

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