CERTARA

Changing the Game in Drug Development

A Selection from Certara's Best of Blogs

Optimizing Drug Development Decisions: Where We've Been and Where We're Going

At the end of the day, it's important to reflect on why we are in the business of drug development decision optimization. The pharma pioneer, George Merck, said it best,

> "We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been."

At Certara, we put patients first and think differently to accelerate drug development and optimize the use of new medicines. We harness our scientific, technological, and regulatory expertise to improve the lives of people.

In 2016, we had the privilege of partnering with our clients on many life-saving or life-enhancing drugs, in therapeutic areas including oncology, central nervous system diseases, infectious diseases, and auto-immune diseases. Our powerful model-informed drug development and regulatory science solutions have helped our clients bring safer and more effective medications to patients in less time and at lower cost.

2017 will be an exciting time for pharma for many reasons. In the US, the 21st Century Cures Act, which includes the President's Precision Medicine Initiative and Vice President's Cancer Moonshot program is expected to pass, opening up additional demand for innovative quantitative pharmacology strategies. Both the Prescription Drug User Fee Act (PDUFA) and Generic Drug User Fee Amendments (GDUFA) renewals highlight model-informed drug development as critical for advancing the industry.

Read the following blog posts for insights from our thought leaders on how modeling and simulation has impacted and is continuing to reshape our approach to drug development.

Revolutionizing Drug Development: d3 Medicine Joins the Certara Family

By: Craig Rayner

Thinking Without Borders™ Developing Medicines that Matter™

These guiding principles fueled the creation of d3 Medicine. With a goal of revolutionizing the pharmaceutical paradigm to accelerate developing medicines that benefit society, combining d3 and Certara was a "no brainer."

Delivering on our clients' missions

The d3 Medicine staff join Certara's Strategic Consulting (CSC) division, which was formed in July 2015 through the merger of Quantitative Solutions and Pharsight Consulting Services. We are now the largest and most transformational consultancy of its kind, with more than 100 scientists, most with PhDs or PharmDs.

d3 Medicine's staff is comprised of experienced drug developers, clinical pharmacologists and regulatory specialists. Our team can advise on all aspects of drug development strategy. Partnering with our clients, we derive a more robust plan that has been pressure tested from multiple angles. We incorporate contemporary thinking in regulatory science, quantitative clinical pharmacology and value-focused decision-making.

Patient health is always at the forefront of our work.

By combining with Certara's unique model-informed drug development and regulatory submittal and communications expertise, we can move forward more quickly on achieving our mission: we are revolutionizing drug development by applying quantitative science and smart regulatory strategy to inform the most crucial decisions.

Specifically, we bring to Certara and its clients expanded capabilities and expertise, most notably in the areas of oncology, orphan diseases, infectious diseases and inflammation, including:

- drug development optimization strategy, stewardship and implementation
- regulatory consulting and liaison services with global health authorities, and
- evaluating, strategizing, and optimizing licensing and M&A plans

Spotlight on the clinical pharmacology road map

As clinical pharmacology comprises more than 50 percent of a drug label, the need to optimize safety and efficacy in drug development is critical. We understand the impact of clinical pharmacology on a drug development program and devise strategies to harness that knowledge toward a more successful program in consideration of:

- the rigors and latest thinking on the part of the regulators
- speed, efficiency, and optimization of the development process
- the competitive landscape and a "pharmacology-to-payer" perspective

We begin with a client assessment, diagnosis and gap analysis. Next, we develop and implement a road map that translates model-informed drug development (MIDD) into the decision-making process and leverages all data to align with that optimized clinical strategy. Our expertise from having sat on both sides of the table at critical regulatory meetings provides confidence in our recommendations on how to best leverage MIDD throughout a program.

We can support specific products, programs or entire portfolios, participate in licensing and due diligence activities, work alongside a drug development team, or serve as that fully outsourced partner.

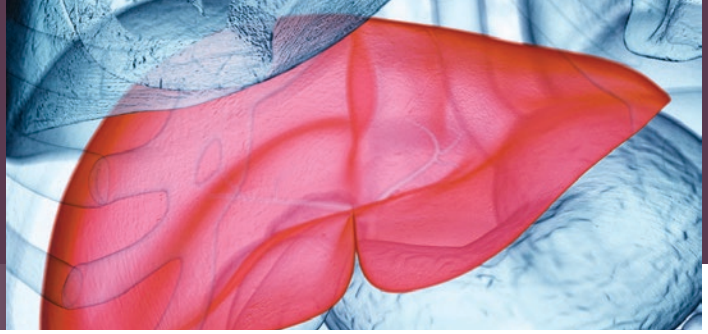
Tailoring a road map to optimize regulatory and commercial success

Our work provides ongoing stewardship for many clients, supporting them at pivotal times during their development programs, including interactions with health authorities, during due diligence or at the deal table with potential commercial partners. Many opportunities to develop medicines faster and better may be unlocked via embracing integrated leadership in clinical pharmacology and regulatory science coupled with advances in pharmacometrics and biosimulation.

Far too many cases treat drug development like a relay race, with the baton handed from one participant to the next. We see it as a team sport where clinical pharmacology helps bring the domains of expertise together in an integrated manner with a renewed focus on regulatory science innovation. We focus on cost, time and certainty, all oriented to the patient need.

Our team of drug development and regulatory science specialists guides the client's program by testing and evolving the strategy to optimize the development program. Moreover, our growing modeling and simulation toolkit, for which Certara has the largest portfolio and client base, further differentiates us. Demand for all of these capabilities is growing exponentially. ■

How to Expedite FDA Approvals of Orphan Drugs



By: Thomas Peyret

350 million patients worldwide suffer from 7,000 rare diseases, yet only 300 of these diseases have approved treatments. This gap, impacting 95% of rare disease patients, represents a huge unmet medical need. Developing drugs for rare diseases poses a range of clinical, regulatory and commercial challenges. The small number of patients are difficult to identify and recruit for clinical trials. Many orphan diseases are genetically based, and oftentimes, these patients have complex phenotypes that react very differently to proposed treatment protocols. The diseases may be poorly understood, making it difficult to set clinical endpoints, biomarkers or outcome measures. Patients may also fall into an ethically sensitive population, ranging from neonates and pediatrics to people with co-morbidities. Modeling and simulation uses disparate information to create a cohesive picture of the dose-concentration-effect relationship that informs development decisions. A recently approved orphan drug exemplifies how pharmacokinetic modeling helped support the approval of a new drug for a rare disease.

Developing a new treatment for a chronic rare liver disease

Primary biliary cholangitis (PBC) is a chronic, rare disease characterized by cholestasis—the impaired flow of bile from the liver.[1] The resulting increased bile acid concentrations cause cellular injury. Untreated PBC can lead to liver failure and death. The only currently approved treatment for PBC was ursodeoxycholic acid (UDCA). However, not all patients respond to UDCA.

Intercept Pharmaceuticals—an emerging global biopharmaceutical company—sought to develop obeticholic acid (OCA) as an alternative treatment for PBC. OCA is a semi-synthetic analogue of the primary bile acid chenodeoxycholic acid with similar pharmacokinetic (PK) properties.[2] Like other bile salts, OCA is metabolized via conjugation to glycine acid and taurine.

OCA is a selective and potent farnesoid X receptor (FXR) agonist.[2] FXR activation decreases the concentration of bile acids in the liver to reduce cellular injury. FGF-19 was used as a biomarker for OCA pharmacological activity.

Understanding the relationship between systemic and hepatic exposure of OCA in PBC patients

Because liver damage is a consequence of disease progression in PBC patients, the Intercept team needed to develop a dosing strategy for OCA in PBC patients with and without hepatic impairment. They conducted a small clinical study wherein a single dose of OCA was given to healthy volunteers and patients with mild, moderate, and severe hepatic impairment and intensive PK sampling was performed for 24 hours.[2]

Study results revealed that systemic OCA concentrations increased with worsening hepatic impairment.[2] Yet, plasma FGF-19 levels were increased with the administration of OCA for subjects with and without hepatic impairment suggesting similar activation of FXR. Clearly, systemic exposure of OCA failed to correspond to its pharmacological effects in the liver. Developing a robust dosing strategy required understanding the relationship between systemic and hepatic exposure of OCA in patients with and without hepatic impairment.

My colleagues and I used our population PK/PD modeling software, Phoenix NLME, to perform physiologically-based pharmacokinetic (PBPK) modeling and simulations.[1,2] The PBPK model was based on a previously reported model for chenodeoxycholic acid.[3] The model for OCA was calibrated using the plasma concentration-time profiles of OCA, glyco-OCA and tauro-OCA in healthy volunteers who received a single dose of OCA. Then, the model was recalibrated for patients with hepatic impairment taking a single dose of OCA. Hepatic impairment involves the following mechanisms which were incorporated into the model: decreased hepatic update of OCA and its metabolites, portal systemic shunting, decreased functional liver volume, and increased taurine conjugation.

The physiologic PK model was validated when its predicted OCA-plasma exposures were found to be comparable to observed exposures in healthy volunteers and patients with hepatic impairment.[2] Both the model and clinical data showed a significant increase in systemic exposure of OCA in patients with hepatic impairment. Yet, liver exposure of OCA was predicted to only increase modestly in patients with mild, moderate, and severe hepatic impairment compared to healthy volunteers. The modeling results and clinical trial data supported the safety and efficacy of the OCA dosing strategy. Dosing reductions were only required for PBC patients with moderate and severe hepatic impairment.[1,4]

Gaining FDA approval

In May 2016, the FDA approved Ocaliva (obeticholic acid) for the treatment of PBC in combination with UDCA in adults who show inadequate response to UDCA alone or as a single therapy in adults who cannot tolerate UDCA.[5] It is the first new drug for PBC in almost 20 years.

Because of Ocaliva's potential to address an unmet medical need, the FDA granted it fast track designation.[5] Ocaliva also received orphan drug designation which entitles its sponsor to tax credits, user fee waivers, and market exclusivity rights. The case of Ocaliva demonstrates how sponsors can accelerate their drug approvals through leveraging pharmacometric modeling. ■

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Modeling and Simulation Guides Dosing for a New Anti-psychotic Drug

By: Karen Rowland Yeo

Drug development is becoming more complex than ever. Regulatory agencies expect sponsors to consider a wide variety of intrinsic and extrinsic factors that could impact drug safety and efficacy. These factors include intrinsic variability—CYP metabolizer status, age, sex, renal/hepatic impairment—as well as external variables—co-medications, food effects, smoker status, etc.

Clinical trials alone simply cannot evaluate all potential scenarios. Using modeling and simulation to conduct virtual trials can help sponsors optimize the dosing strategy and label claims for their drug programs. In this blog post, I'll discuss how we used modeling and simulation to help a sponsor develop a new treatment for schizophrenia.

Improving medication adherence through a new formulation of an anti-psychotic

Despite the availability of effective treatments, schizophrenia patients frequently relapse due to poor medication adherence. Thus, Alkermes developed aripiprazole lauroxil (AL), a novel long-acting injectable (LAI) atypical anti-psychotic drug.[1] Administration of AL results in extended exposure to aripiprazole, and allows for multiple dose strengths and dosing intervals, which provides flexibility for individualized patient care.

Following injection, aripiprazole lauroxil is converted to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole, the active drug. Aripiprazole is primarily eliminated by the drug metabolizing enzymes CYP2D6 and CYP3A4.

Understanding the impact of concomitant medications

AL was designed to be injected either every four (at three possible dose levels) or six weeks at the highest dose level. The drug development team at Alkermes needed to understand the impact of concomitant administration of strong CYP3A4 inhibitors and inducers and strong CYP2D6 inhibitors on AL pharmacokinetics (PK). Since CYP2D6 poor metabolizers (PMs) have a reduced ability to eliminate CYP2D6 substrates, they also wanted to know if these patients required dose adjustments.

Using PBPK models to predict the impact of concurrent medications

Physiologically-based pharmacokinetic (PBPK) models describe the behavior of drugs in the different body tissues. Depending on the route of administration, the course of the drug can be tracked through the blood and tissues. Each tissue is considered to be a physiological compartment. The concentration of the drug in each compartment is determined by combining systems data, drug data, and trial design information. The systems data includes demographic, physiological, and biochemical data for the individuals in the study population. The drug data consists of its physicochemical properties, its binding characteristics, and information on its metabolism and solubility.

The trial design information comprises the dose, administration route, dosing schedule, and co-administered drugs.

The Simcyp Simulator PBPK platform was used to predict the impact of co-administration of CYP3A4 and CYP2D6 inhibitors/inducers on aripiprazole exposure in patients with varying CYP2D6 metabolizer status.[2]

Informing the dosing strategy

Results from the PBPK model suggested that reduction of the high and medium dose to the next lower dose in the presence of strong CYP3A4 and CYP2D6 inhibitors is needed to keep aripiprazole exposure in the target range.[3] Likewise, in the presence of a strong CYP3A4 inducer, the low dose needs to be increased to the next dose level to keep aripiprazole exposure within the therapeutic window.[3] The PBPK model also helped to make recommendations on dose adjustments for CYP2D6 PMs who were also taking strong CYP3A4 inhibitors.[3]

Aristada (injectable, extended-release aripiprazole lauroxil) received FDA approval in late 2015.[4] Dose adjustments in the drug label were based on simulations that examined the effects of co-medications on aripiprazole PK. The effect of patients' CYP2D6 genotype was also incorporated into the PBPK model and informed label claims. The insights from modeling and simulation approaches as well as the product characteristics of AL provide clinicians with flexibility in devising safe and effective treatment plans for schizophrenia patients who have difficulty with medication adherence. ■

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How Biosimulation Can Bring New Immuno-oncology Treatments to Patients

By: Rik de Greef

Immuno-oncology, which harnesses the patient's own immune system to fight cancer, is one of the hottest areas in drug development today. In recent years, the FDA has granted breakthrough therapy designations to multiple immuno-oncology drugs for a variety of oncology indications including advanced non-small cell lung cancer and melanoma. Over the last two decades, PK/PD modeling and simulation (M&S) has played a growing role in oncology drug development. In this blog post, I'll discuss how M&S (also known as biosimulation) can help support some of the unique challenges that immuno-oncology programs face.

A 21st century treatment with 19th century roots

When it comes to immuno-oncology treatments, everything old is new again. In the late 19th century, an intrepid physician named William Coley was struck by the case of a deathly ill cancer patient who made a seemingly miraculous recovery after contracting a serious bacterial infection. This strange case inspired him to deliberately infect another cancer patient with bacteria. Again, the patient who was suffering from an advanced-stage sarcoma, recovered. Dr. Coley kept refining his treatment, known as Coley's toxins. A lack of understanding of the immune system meant that no one knew exactly how this treatment worked. Eventually, Coley's toxins fell into disuse with the emergence of radiation therapy in the early 20th century.

How the immune system targets cancer cells

In addition to protecting us from pathogens, the immune system is also able to identify and destroy cancer cells. Briefly, the cancer-immunity cycle works as an interplay between T-cells and tumor cells. When tumor cells die, they release antigens which trigger the activation of specific T-cells. These migrate into the tumor where they can kill tumor cells, thus causing a further release of antigens, serving to maintain the cycle.

How do immunotherapy drugs rev up the immune system to fight cancer?

Immuno-oncology drugs bind their pharmacological targets to stimulate the immune response. Many of these targets have a general role in immune system. Drugs that are selective for these targets risk causing systemic immune-related adverse reactions. On the other hand, there are several pharmacological targets which are specific to the T-cell/tumor interaction, eg, PD-1/PD-L1.

PD-1: A key immune checkpoint in cancer

PD-1 (Programmed cell death 1) is a protein that serves as an immune checkpoint. It downregulates the immune system by preventing the activation of T-cells. PD-1 helps reduce autoimmunity and promotes self-tolerance. This checkpoint protein inhibits the immune system by promoting apoptosis in antigen specific T-cells and, simultaneously, reducing apoptosis in regulatory T cells (suppressor T cells). Cancer cells overexpress PD-1 ligands (PD-L1/PD-L2) which bind PD-1 and thereby suppress the immune system.

Immuno-oncology drugs can target the PD-1 signaling pathway in one of two ways. PD-1 inhibitors target PD-1 on T cells whereas PD-L1/PD-L2 inhibitors target the PD-L1/PD-L2 ligand expressed on tumor cells. These inhibitors are generally antibodies. Both types of inhibitors release the "brakes" that the tumor places on the immune system so that T-cells are able to identify and kill cancer cells.

The pharmaceutical industry has jumped on the "PD-1 bandwagon." Two anti-PD-1 drugs (nivolumab and pembrolizumab) have been approved and at least nine other PD-1/PD-L1 drugs are in varying stages of clinical development. Likewise, a rising trend is to combine immuno-oncology drugs with other anti-cancer treatments including standard chemotherapies, targeted therapies, other immuno-modulators, and anti-cancer vaccines.

Clinical results of anti-PD-1 treatments are promising

Initial clinical results of anti-PD1 treatments have been promising. Objective response (OR) rates have been observed in multiple cancer types that are well beyond the rates achieved with present standard of care (SOC). In the meantime, these drugs have also demonstrated clear improvements in overall survival (OS) for cancer patients. Specifically in advanced melanoma, superior efficacy was observed in comparison to dacarbazine, the pre-immunotherapy SOC, as well as in comparison to ipilimumab, a CTLA-4 inhibitor and the first immune checkpoint inhibitor. Patient PD-L1 status appears to predict the response to anti-PD-1 drugs. Since PD-1 inhibitors block the interaction between PD-1 and its ligands expressed on tumor cells to "revive" the immune system, it's no surprise that patients with PD-L1 positive tumors consistently have better outcomes than PD-L1 negative patients.

Clinical development in immuno-oncology

The standard clinical development trajectory follows a phased, linear course. Clinical pharmacology characterization is largely done through dedicated healthy volunteer studies in Phase I. For these programs, M&S is applied in learn-confirm cycles which inform the next phase of development and generally take place around well-defined milestones in the program.

In contrast, clinical development in immuno-oncology programs thus far has followed a much more condensed time line wherein the classical drug development phases are not readily discernible. Clinical pharmacology is generally characterized as part of safety/efficacy studies rather than through healthy volunteer studies. In this compressed time line, modeling and simulation is continuously applied to address a variety of questions; no clear separation exists between learn-confirm cycles.

Key challenges and opportunities in immuno-oncology clinical development

The unique trajectory of immuno-oncology programs means that their sponsors face distinct challenges. For example, the time lines for development tend to be highly condensed by the opportunity for fast-track approval. In addition, a lack of early clinical biomarkers means informing dosing using early clinical data is difficult.

Immuno-oncology has its upsides as well. Opportunities frequently arise for extending the drug to multiple oncology indications. M&S can help leverage the data from one indication to support development, and ultimately, approval for another. Moreover, the potential for developing multiple combination treatments can increase the value of a drug program.

How can PK/PD M&S be applied to immuno-oncology?

PK/PD modeling and simulation can be leveraged throughout the development of an immuno-oncology drug. Early in development, M&S can help translate preclinical data from mouse xenograft models to support establishing the clinical dose regimens. Once a drug candidate moves into the clinic, its safety and efficacy profile must be characterized. Pharmacometrics can help establish the relationship between drug exposure and safety and efficacy parameters to support and justify the dosing regimen and determine the drug's therapeutic window.

Regulatory agencies expect sponsors to understand the intrinsic and extrinsic factors that might cause variability in drug exposure. In the absence of dedicated clinical pharmacology studies, population PK analysis can be performed on sparsely sampled PK data from patients to understand which factors significantly impact exposure. Furthermore, semi-physiological approaches can be used to predict PK at the site of action. These models can also help predict PK in other populations that the sponsor might want to include in the drug label.

Finally, regulatory success alone is no guarantee of commercial success. By understanding the competitive landscape, sponsors are better positioned to make critical decisions. Model-based meta-analysis (MBMA) of publicly available clinical trial data can be used to assess a compound's safety and efficacy profile compared to the SOC and/or competitor drugs in development. MBMA enables indirect comparison, taking into account the impact of treatment, patient population, and trial characteristics. This type of analysis can help estimate the probability that a drug can differentiate itself in terms of efficacy and/or safety from competitors in the same drug class or across drug classes. In the quickly evolving immuno-oncology landscape, MBMA and associated clinical trial outcome databases allow sponsors to stay on top of new developments and understand the relative merits of their drug.

Immuno-oncology drugs have the potential to serve as a powerful weapon in the war on cancer. By leveraging modeling and simulation approaches, sponsors have the ability to maximize their likelihood of regulatory and commercial success. ■

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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

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