CERTARA

Best of the Blog 2017

Introduction

We are what we repeatedly do. Excellence, then, is not an act, but a habit.

—Will Durant

What gives you a sense of purpose in your life? At Certara, we're driven by our mission: Enable superior drug development and patient care decision-making through model-informed drug development, regulatory science and knowledge integration, thus optimizing R&D productivity, commercial value, and patient outcomes. And in our blog, our passion for scientific excellence and thought leadership shines brightly.

If "excellence is a habit," then 2017 was a most excellent year for our blog. After three years of posting weekly, we've hit our stride in sharing stories on our biggest challenges and accomplishments in regulatory strategy, modeling and simulation, and regulatory writing.

So, get a comfy chair, maybe a cup of coffee, and enjoy the highlights of the Certara blog. Remember to visit us online at Certara.com where we can continue the conversation about how to leverage technology and pharmaceutical science to optimize your most critical drug development decisions.

Suzanne Minton, Certara Blog Editor in Chief

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Educate to Influence: Shaping Critical Drug Development Decisions

At Certara, we believe in the value of "educating to influence." Thus, we're not just a *technology-enabled* company. We're a company composed of excellent communicators who are masters at explaining how these technologies inform our client's most critical development decisions.

The blog posts in this section address some of the latest approaches being leveraged in drug development, and how they can help sponsors save time and money. There is also a blog post on tips for being a better presenter in virtual settings. We hope that you enjoy them and find them useful.

Speaking into the Ether: Challenges of the Virtual Pharma Workplace

Peter Bonate and Stacey Tannenbaum

In today's global pharma working environment, virtual interactions are sometimes more common than live exchanges. Many people work virtually through teleconferences, video conferences, instant messaging, phone calls, and emails. Through flexible schedules and working remotely, some people spend the majority of their day without seeing or hearing their colleagues.

Honing your skills

Pharmacometricians are like consultants; they tend to be influencers rather than primary decision-makers in the drug development process. Therefore, the most important skill for pharmacometricians is not the ability to analyze data but rather to present evidence effectively. Here are some useful tips to improve your presentation performance.

Challenging assignment

Speaking into the ether—or giving a virtual presentation—is tough. It's almost like presenting to an empty room! Engaging a virtual audience can be very difficult. It's hard for you, as the presenter, to keep your energy level high without feedback. Furthermore, the audience knows you can't see them—you are just a disembodied voice—and so it's easy for them to tune out and do other things.

Engaging your audience

To retain your audience's attention—and dissuade them from multi-tasking—you need to be more interesting than everything else that is going on around them.

In one survey, 90% of 385 respondents admitted to engaging in other activities instead of paying attention during a conference call. Those activities ranged from doing unrelated work (60%), answering email or instant messenger (50%) and eating (40%) through to changing clothes (4%), preparing meals (2%), and napping (1%). Attendees multi-task for many reasons—they are impatient, they are busy, their laptop is right in front of them (so why not), they feel as if they are getting more done, or they are bored.

An audience's attention level tends to be high at the start of the presentation, wane towards the middle, and then pick up near the end. Break up your talk so that your audience's attention is more like a sine wave, which fluctuates between peaks and nadirs, so the audience can naturally ride along with you.

You need to grab their attention right away with your content. State your message or conclusion at the start of each slide and then follow up with your rationale. Try some new or interesting graphics—such as "catter plots" (scatter plots that use cats instead of points as symbols) or take the lead from a fire science team who used flames as the backdrop for their plot.

Consider using interactive or dynamic graphics instead of static ones. Use an R Shiny app, for example, to show simulations in real time. Video clips and gifs also help to capture audience attention. Consider annotating your slides on the fly or using a mouse or on-screen pointer to highlight a word or phrase. Animation is also a great addition (used judiciously!). If your webinar tool doesn't support animation, try using PowerPoint builds instead; stacked slides can appear a lot like animation.

Virtual presentations also don't have to be one-way streets. We recommend employing a variety of strategies to engage your audience throughout the presentation. For example, ask attendees to use the chat box or instant messenger to share comments and pose questions throughout the presentation. Create a Twitter hashtag to encourage discussion about the content and include polls or surveys in the deck so you can learn more about your audience and their interests.

Develop a quiz or contest based on your presentation to spur friendly competition and lead to bragging rights or prizes at the end the session. It can be as simple and fun as counting the number of cats that appear in the slide deck!

And try to include personal touches to remind them that there is a real, genuine human being behind the slide deck. Showing a photo of you, seeing your face on video, or telling a personal story or self-deprecating joke all help the audience relate with you. The audience members may be more inclined to listen if they feel like they connect to the presenter.

Rising to the occasion

You are your own secret weapon. Audiences respond not only to your content but also to how you present it.

Learn to leverage your voice. Stand up straight when you are presenting—good posture will make you feel empowered, give you more energy, and make your voice sound stronger. Smile—even though they can't see you—they can hear the smile in your voice.

Practice modulating your speech—change the speed, rhythm, word duration, and volume. Don't be afraid to pause; it adds weight or emphasis to your point. Also, people pay more attention when you suddenly speak louder. Reading a book to children also provides an excellent opportunity to try modulating your voice, pitch, and volume.

Practice with a voice recorder so you can hear how you really sound to an audience—yes, that IS how your voice sounds!

Practice, practice, practice

There really is no substitute for practicing your presentation in front of a live audience. It will allow you to see when they are smiling, spot

any confused looks, determine when their interest wanes, and learn whether they are going to laugh at your jokes. This real-time feedback will enable you to tweak your presentation to ensure that your virtual audience will remain engaged.

And definitely do not read out your slides; you will lose your audience's attention immediately. The content should be used as a framework and not a script. To make the flow feel natural you need to practice.

Extroverts are particularly prone to skipping practice because they assume they can "wing it." They can't. Without practice, they don't know where the natural breaks and transition points are in their presentation, and they haven't thought through what comments they want to make on each slide.

Avoiding technical glitches

While it may not be possible to avoid every technical issue when conducting a presentation online, doing a dry run beforehand will certainly allow you to spot many of them. Ask a colleague to log in as a participant for your test run to make sure that the audience can see what you want them to see. Ask your colleague to check that the animation and video clips run smoothly, they can see the whole slide, and the chat, survey, and annotation tools work for them. Make sure that your scientific formulae render correctly. Also, inquire whether there is a time lag on the presentation. If so, you may want to slow down the pace of your delivery.

Another rule of thumb is to share only one program or document if possible (such as PowerPoint or the PDF of your presentation). If you must share your monitor, close all programs except the ones you are sharing. Close all programs with pop-up windows such as instant messenger or chat, email, and calendar. If you have a dual desktop, make sure you share the correct screen. If you want to share an Internet page, pull it up in advance and close all other tabs. Also, be careful to remove any company intellectual property or personal information from your desktop. Once the presentation is over, don't forget to STOP sharing your desktop!

Preparation is the key to a strong presentation. Plan for all eventualities including IT failure. Have a copy of your presentation printed, and also saved to the cloud and on a thumb drive. Make sure that your laptop or other devices you need for the presentation are charged beforehand. Turn off your phone. If you plan to give a demonstration, make sure that you have screen shots which convey the most important points in PowerPoint slides as a backup.

And if all else fails, laugh! Things do go wrong sometimes and humor will help your audience to empathize with you.

Summary

Strive to keep your presentation dynamic and interesting. The challenge is even greater with a virtual presentation when you can't see or hear your audience, and they can't see you. Learn to master all the presentation tools, particularly those which allow interaction with the audience, whether it's the chat function or annotating slides. Don't just project a slide show!

And most importantly: practice—that is the best way to overcome your natural fight-or-flight response and optimize your skills! Good communication skills are now a vital asset for successful pharmacometricians. ■

How MBMA Can Help You Make Smarter Drug Development Decisions

Leon Bax

Successful drug development depends on making wise decisions about portfolios, clinical trials, marketing, etc. We're continuously faced with the challenge of deciding whether to continue development or stop it. To support those decisions, we gather data, typically through clinical trials. We analyze the data from those clinical trials, and then we use these analyses to build models that we then use to predict what may happen in the next trial. The data collected from these in-house trials are "internal data" or "proprietary data."

In addition to your internal data, external data are accessible through many sources including published articles in PubMed, the FDA website, and ClinicalTrials.gov. Using external data to aid decision-making is cost-effective because your competitors have already paid for the research to generate the data. But, perhaps more importantly, using external data is necessary to inform key decisions.

Combining aggregate level data from multiple studies

Companies rarely share individual level data. But, they all publish most of their aggregate level trial results. Meta-analysis is the statistical method for combining data from multiple studies. Preferably, you perform a meta-analysis on data from systematically searched and selected sources, collected in an actively maintained database. This full process is a systematic review or evidence synthesis.

An introduction to meta-analysis

Meta-analysis requires data aggregation. What does that mean? Each clinical trial has a number of patients in them. Some trials have more subjects than others. And each subject in each trial will contribute one or more data points regarding the effects of a drug. Each patient will also contribute information regarding covariates such as age, body weight, etc.

The process of aggregation summarizes these data. So for each of these trials, we summarize the drug effects and covariates. In addition, we give more importance to the bigger trials than to smaller trials in

the analysis. Thus, we assign each study a weight, typically based on the inverse of the variance. That means that we integrate the size of the trial, the number of subjects, as well as the variability in the trial.

When we run our meta-analysis, we combine statistics from different trials to identify a parameter that describes the effects in these trials. A regression analysis could also be performed to describe how covariates —a drug, dose, or demographic factor—impact that drug effect.

The historical context for meta-analysis

Gene Glass, a social scientist, introduced the term meta-analysis in the mid-1970s. And meta-analysis is still heavily used in social sciences, not just in medicine. In 1904, Karl Pearson was one of the first to statistically combine medical data from previous analyses of the inoculation of soldiers to prevent typhoid fever.

Since the 1990s, meta-analysis has become a cornerstone of evidence-based medicine. Most meta-analyses in the medical literature evaluate the effects of approved drugs. Over the last ten years, using meta-analysis to support drug development decisions has increased in popularity.

Types of meta-analysis in drug development

Several different types of meta-analysis are used to inform drug development. The most utilized type of meta-analysis is pairwise meta-analysis, which examines interventions or trial arms in pairs. This approach has the advantage of being relatively fast and easy. The major drawback to pairwise meta-analysis is that it only considers paired intervention-versus-control evidence. Thus, it cannot make indirect comparisons of drugs that haven't been compared in a clinical trial.

Network meta-analysis combines studies in a network and builds a statistical framework to support indirectly comparing drugs that may not have been evaluated head-to-head in clinical trials.

Model-based meta-analysis (MBMA) extends upon network meta-analysis. MBMA combines information on a drug given at multiple doses and time points as well as multiple drugs with the same mechanism of action in a statistical framework that integrates models inside models. This framework enables "borrowing information" across different trials or different drugs. MBMA incorporates dose and duration and uses standard pharmacology models and assumptions. It can include trial-level covariate relationships on the dose-response models to account for between-trial differences in patient populations. It also allows us to simultaneously model multiple endpoints and potentially link biomarkers to clinical outcomes.

Like network meta-analysis, MBMA can provide indirect comparisons. However, because MBMA uses longitudinal dose-response models for individual drugs or drug classes and incorporates covariate effects in these models, we can use MBMA to evaluate new scenarios and simulate the probability of clinical trial success.

What questions can be answered with model-based meta-analysis?

MBMA can answer questions related to your program's competitive landscape, disease/trial characteristics, and drug characteristics.

You may want to know the key comparators or key competitor compounds in a certain therapeutic area. Or you might wonder how many trials are available for a specific endpoint.

You can also use MBMA to gain insights into disease pathology and clinical trials that have been conducted in that indication. This approach can reveal the major covariates for trials in terms of populations, baseline values, and demographics. In addition, you can examine typical placebo effects and their variability. And, you can evaluate the heterogeneity within outcomes and how the trials were conducted.

Lastly, MBMA can provide competitive intelligence on the dose-response and time-course of drugs in the same class or other classes. Ultimately, these models can help you differentiate and position your drug between existing and developing competitors.

While some of these questions can be answered with internal (proprietary) data, most require external data.

Take home messages

MBMA combines aggregate level data from published sources in a formal, quantitative framework. These aggregate level data are typically attained from published articles in PubMed, ClinicalTrials.gov, the FDA website, and scientific conferences.

This innovative approach can help answer key questions in drug development. We can leverage MBMA to predict Phase 3 trial results including comparisons of drugs that were not compared in trials before. Multiple endpoints can be modeled, even simultaneously, and multiple scenarios with those endpoints can be assessed in simulations. We can use those simulations to predict the probability of a drug being superior or non-inferior to a competitor in a head-to-head clinical trial. The insights gained from MBMA can be used to optimize clinical trial designs and marketing/commercial strategies. ■

First-in-human Trials and Going Too FAAH from the Sentry

Graham Scott

Many people in the UK and elsewhere remember where they were and what they were doing on the day that Diana, Princess of Wales, died: August 31st marks 20 years since that fateful day.

For clinical pharmacologists, we may well remember where we were when we heard the news that six volunteers were fighting for their lives in a hospital in West London following administration of a test drug in a first-in-man study. I was on a train passing through the leafy Sussex countryside when I heard the news on the evening of March 14th, 2006. The trial was with TGN1412: a humanized monoclonal antibody that binds to and is a strong agonist for the CD28 receptor. The agent was under development by TeGenero. Mercifully, all the volunteers survived but not without life-changing injuries.

The event certainly changed the conduct of early phase clinical trials. Regulators were swift to issue new guidance (EMA, 2007). It was helpful for our industry to be scrutinized by the outside world: practices that we had no longer questioned as they were "industry standard" were suddenly exposed to public scrutiny. Among the many valuable recommendations for study conduct and design, one lesson stood out to me: *don't dose a cohort of subjects simultaneously.* Had just one volunteer in the TeGenero trial been dosed with active drug and observed before the rest of the cohort were dosed, the impact of the adverse event would have been dramatically reduced.

At the time, the "standard approach" was a 6+2 (6 active subjects and 2 placebo) dosed simultaneously. The EMA 2007 guideline (issued in response to the disaster) called for sequential dosing in which... *it will usually be appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP (Investigational Medicinal Product).* The same concept is captured in the 2017 revised guidance (EMA 2017) in which the term "sentinel" dosing is now commonly used and understood.

Strangely enough, our community used to use the sentinel approach in the 1980s. In my first few years in the industry, I travelled to a Phase 1 unit in Dundee, Scotland to assist in 14C ADME studies. The unit at that time adopted a "lead volunteer" approach for single rising dose studies. The study design was published in 1989 (McEwen 1989 and see below)—I suspect we could use the same design now and be fully aligned with the EMA's most recent guideline. In fact, it's a more elegant design than some of the new standard sentinel designs. Perhaps a question for the historians (and us all): why did we forget, and why did it take a disaster to relearn what we once knew?

Table 1: Design of a typical ascending dose pilot Phase 1 study involving 26 subjects in five separate double-blind study sessions*

		Dosage Level			
Week	Placebo	1	2	3	4
1	1	1	–	–	–
2	1	4	1	–	–
3	1	–	4	1	–
4	1	–	–	4	1
5	1	–	–	–	5
Total	5				

*from *Xenobiotic Metabolism and Disposition: The Design of Studies on Novel Compounds* (McEwen, 1989, "Studies in Man with Potential Therapeutic Agents").

Note: On each occasion, one subject in the group receives placebo and only one subject receives the "leading" dose.

More regrettably, a healthy volunteer died in another early phase clinical trial conducted almost a decade later. In 2007, there was some acknowledgement that the study drug was "new" in the sense that it was a monoclonal antibody with stimulatory activity. Not so this time. The Portuguese company Bial had developed a conventional small molecule, and serious adverse events weren't expected to occur in the trial: the pharmacology was known and small molecules in the same class (FAAH inhibitors) had already been studied in humans. Extensive toxicology studies had been conducted—in greater duration and extent than stipulated by regulatory guidelines: three months' toxicology in mouse, dog, and monkey and six months in rat. The early part of the study went well: a single rising dose phase (with a sentinel dosing approach) in eight cohorts, a food effect cohort had been conducted, and no less than four multiple dose cohorts (treatment once a day for 10 days) had been successfully completed.

But on the 5th day of the final multiple dose cohort, things started to go wrong. On Sunday evening of January 10th, 2016, one subject was admitted to the hospital with a suspected stroke that was not considered to be drug related. On Monday morning of January 11th, the news on the hospitalized subject was positive, and the remaining volunteers were dosed for the 6th day of administration. During that day, the condition of the hospitalized subject deteriorated, and he fell into a coma. The study was stopped. In the following few days, four other subjects developed neurological symptoms, and at 13:25 on Sunday, January 17th, Guillaume Molinet, an artist and father of four children, died aged 49.

Undoubtedly, many valuable lessons have already been learned from this tragedy; the revised EMA guideline is as good an expression of these lessons as any.

Whilst the cause of the toxicity observed in the Bial trial remains uncertain, off target effects unique to the test drug were likely involved. Van Esbroeck et al (2017) concluded from *in vitro* studies that "promiscuous lipase inhibitors (such as BIA 10-2474) have the potential to cause metabolic dysregulation in the nervous system." Extensive studies of potential off target effects thus must be conducted with more rigor than that done by Bial. This is especially true for agents that bind irreversibly (as FAAH inhibitors do) and for agents that bind to targets that are members of large families such as serine hydrolases.

For me, there was one prominent study design learning: *don't dose higher than necessary.* In the 1980s, one of my colleagues described a "first-in-man single rising dose" study (with his tongue only partially in his cheek) as a "poisoning study." He meant that the trial's objective was to escalate the dose until toxicity was observed, thus allowing the "maximum tolerated dose" (MTD) to be discovered. Sadly, this thinking has remained ingrained in the minds of "first-in-man" practitioners despite critical commentary. After the TeGenero accident in 2006, Cohen wrote an "Editor's View" entitled, "Should we tolerate tolerability as an objective in early drug development" (Cohen, 2007). He argued that early drug development is about pharmacodynamics and pharmacokinetics and should be powered for these primary objectives rather than tolerability. The recent guidance issued by EMA also advocates this reasoning (at least for healthy volunteer trials): "A trial design using a MTD approach is considered to be inappropriate for healthy volunteers." In hindsight, which is indeed a wonderful thing, it seems that had the designers of the trial with BIA 10-2474 been more conscious of exposure response relationships and less concerned with MTD, they may well have decided that the top multiple dose cohort was unnecessary. Whilst first-in-human trials do need to explore high exposures to gain confidence to proceed to studies in larger, more diverse populations, a conscious decision on the upper acceptable exposure needs to be made by blending *a priori* knowledge with accruing data from the study itself.

The lesson from this most recent tragedy is that understanding exposure response relationships is much more informative for drug developers than attempting to define MTD, and it happens to be safer too. ■

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Mind the Gap: Best Practices in Clinical Pharmacology Gap Analysis

Julie Bullock

Do you get anxious about taking tests? Many people do because they want to show their best efforts.

Submitting your New Drug Application (NDA) to the FDA can be thought of as the ultimate test of a drug program. Are you confident that you'll have robust answers to the 40 different questions that the agency will ask about your clinical pharmacology data package at the time of a NDA submission? If the thought gives you "pre-test jitters," you might want to invest in clinical pharmacology gap analysis—a tool that can help you evaluate and address any potential gaps in your program *before the FDA does.*

What is gap analysis?

Creating a clinical pharmacology strategy involves assessing a sponsors' development program across multiple domains to craft a strategy to address each. For a target product or program, the strategy includes the following elements:

- Identifying potential R&D or regulatory challenges, custom to the molecule, therapeutic area, and competitive landscape
- Ensuring integration of pre-clinical findings with planned clinical programs
- Creating a clinical pharmacology development program in line with anticipated regulatory filing strategy
- Identifying and leveraging pharmacometrics and other model-informed drug development technologies that will increase speed and efficiency
- Guiding interactions with regulatory agencies for research programs and submittals

The first step in a strategic assessment is a gap analysis. In conducting a program gap analysis, we consider the 40 different questions that the agency will ask about your clinical pharmacology data package at

the time of a NDA submission. This allows one to evaluate and address any potential gaps before the FDA does at critical milestones such as End of Phase 1 (EOP1), EOP2 or Pre-NDA while ensuring that your NDA will contain all the elements needed to support review and informative actionable labeling for your product. In addition to identifying gaps and hot spots, a clinical pharmacology development strategy is created to ensure each of the relevant domains are covered, that gaps are properly addressed, and that data is gathered at meaningful times to enhance decision-making during development. While best conducted early, a gap analysis provides unquestionable ROI at any stage of development.

Reducing the uncertainty of drug development

A group from the US FDA, academia, and industry recently wrote a paper articulating how clinical pharmacology methods and quantitative frameworks can improve the efficiency of drug development and evaluation.[1] That 2017 *Clinical Pharmacology and Therapeutics* paper, "Improving the Tools of Clinical Pharmacology: Goals for 2017 and Beyond," attributes the limitations in drug development to scientific challenges in predicting efficacy and safety or characterizing sources of response variability for a drug compound at early, less expensive stages of discovery.[1]

The field of clinical pharmacology can help stakeholders address these challenges and improve decision-making at critical milestones, whether early in proof-of-concept phases (pre-clinical through 2a) or in the later stages where a more robust risk and efficacy profile is established (2b through 3). The tools, methods, and frameworks (eg, mechanistic or quantitative) of clinical pharmacology span distinct sub-specialties and can significantly impact these pre-clinical and clinical phases. They can greatly reduce uncertainty related to therapeutic targets, dosing, and patient populations in which the novel compound may have the most efficacy.[1]

Clinical pharmacology comprises about 50% of a drug label. Its importance in drug development and clinical decision-making is undisputed. These principles guide our approach to gap analysis.

The clinical pharmacology review process

FDA's Center for Drug Evaluation and Research, Office of Clinical Pharmacology (OCP) recently updated its Manual of Policies and Procedures (MAPP) Good Review Practices for New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs). The MAPP includes guiding principles for the OCP integrated review, specific templates and sections for review, a guide for labeling issue identification, and a clinical pharmacology and pharmacometric summary table. OCP reviewers use the Question Based Review (QBR) outlined in the MAPP to guide NDA and BLA reviews.

Clinical pharmacology is a multidisciplinary science. Thus, OCP reviews of NME NDAs and original BLAs synthesize information from relevant areas including drug disposition, pharmacology and biomarkers, quantitative methods, drug safety, drug efficacy, pharmacotherapy, and clinical trial methods to inform regulatory decisions (eg, approvability, labeling, post-approval requirements, and product lifecycle management).

Pharmacometric analyses are a key component of each question in the OCP QBR and are used to:

- Support drug activity
- Identify subsets of patients with notably large treatment benefits or favorable risk/benefit balance or a drug with significant toxicity or otherwise marginal average treatment effects
- Support a single adequate and well-controlled clinical trial using dose-response and/or exposure-response trends
- Support the dosing regimen
- Identify intrinsic factors that influence exposure and/or PD of the drug
- Support a dosing strategy based on modeling and simulation
- Justify dosing for subgroups and specific covariates (age, weight, renal/hepatic)

The OCP review is issue-driven and assesses information in the applicant's submission with established knowledge to address dose selection and optimization, therapeutic individualization, and benefit/risk balance for the general population and for subpopulations. The OCP review also identifies critical gaps in the understanding of conditions for optimal therapeutic use and recommends studies that can address those gaps. Established and evolving regulatory policies and practices guide OCP recommendations.[2]

The purpose of gap analysis

We help position sponsors for successful interactions with regulators and other partners by creating for them a clinical pharmacology and pharmacometrics roadmap that prioritizes needs, provides strategic direction, identifies gaps, and assesses risk/benefits. The strategic plan will be harmonized with the sponsor's overall clinical development plan and considers strategies to support breakthrough therapy applications and accelerated versus regular approval pathways. In all scenarios, the gap analysis and strategic plan identifies and mitigates risks which could become either decision-making hurdles during development or regulatory hurdles at the time of approval.

A gap analysis begins with evaluating all available data and information on the compound, including the Target Product Profile (TPP), Investigator's Brochure, clinical study plans, any regulatory meeting minutes, and all available pre-clinical and clinical technical data. A gap analysis report will outline the clinical pharmacology program needs, assess which dedicated studies are needed and why, and recommends the use of pharmacometrics and other quantitative methods to expedite timelines, reduce cost, and minimize clinical studies wherever possible.

Questions asked and answered in a gap analysis include:

- Will the completed or planned studies support the OCP question-based review (QBR) and labeling?
- Are the data collected sufficient to support planned analyses?
- Does the quality of existing data, analyses, study designs, and overall clinical approach support the desired regulatory strategy?

- Are we leveraging the "best" science and technology available?
- Does the data support the goals of the TPP?
- Is more evidence needed? If so, is it better to obtain this evidence through standalone studies or through quantitative analyses?

The gap analysis summary report will provide the sponsor with a plan to address any clinical pharmacology gaps and recommend strategies for submitting a data package for regulatory approval. Gap analysis can be performed in early development, in advance of the IND submittal, in mid-development, either for the End of Phase 1 or End of Phase 2 meeting, or later in development, as a company prepares the NDA or BLA submission.

The return on investment (ROI) of gap analysis

A gap analysis provides a roadmap for success, translates model-informed drug development (MIDD) into the decision-making process, and identifies ways to either support or supplant clinical studies. The areas for which MIDD can be leveraged include drug-drug interaction (DDI) strategy, the approach to support dose justification based on pharmacokinetic/pharmacodynamic (PK/PD) and exposure response, the strategy to meet evolving requirements for QTc assessment, the plan for addressing special populations (renal/hepatic impairment), and opportunities for pharmacogenomics. Our staff of 550 professionals has years of development experience in FDA and in both large and small pharma. They are eminently capable of performing these analyses. While maintaining regulatory standards, we create efficiencies through better study designs and integrating of MIDD and other technologies. Because we've sat on both sides of the table at critical regulatory meetings, we are confident in our recommendations. Typically, the ROI for this analysis is 10–20x, and frequently 50–100x or more, depending on the program. The ROI includes reduced study size, expedited timelines, and studies that can be replaced by MIDD. For example, our work in physiologically-based pharmacokinetics (PBPK) has achieved more than 100 label claims without the need for clinical studies.

Modeling and simulation—a "useful predictive tool"

Understanding and selecting the correct tool to answer key drug development questions and optimize decision-making is key. Our portfolio of tools in performing a gap analysis and recommending a strategic roadmap include:

- **Drug development and regulatory strategy consulting**—As the industry migrates from a "best in class" to a "best in value" perspective, sponsors' scientific, regulatory, and commercial strategies must be well-aligned. An integrated decision support system focuses on increasing confidence, understanding all aspects of safety and efficacy, optimizing cost and development time, and guiding development using model-informed drug discovery and development (MID3).
- **Pharmacometrics modeling**—Population PK, exposure-response and disease-state modeling are used to predict clinical outcomes, provide support for dose recommendations, justification and modification, assess trends for safety and efficacy across exposure ranges, and inform 'go/no go' decisions.
- **PBPK**—PBPK technology informs key R&D decisions related to clinical trial design, informs first-in-human dosing, formulation design, dosing in special populations, and predicts the likelihood of DDIs.
- **Clinical pharmacology**—Accounting for about 50% of a drug label, clinical pharmacology approaches can reduce late-stage attrition and increase pharma R&D productivity. Expertise in this discipline allows drug developers to reduce uncertainty related to therapeutic targets, dosing, and the patient populations in which the novel compound may have the most efficacy.
- **Quantitative systems pharmacology (QSP)**—This emerging mechanistic modeling approach focuses on target exposure, binding, and expression. It is employed to identify biological pathways and disease determinants.
- **Quantitative systems toxicology (QST)**—QST modeling combines toxicity and "omics" data to focus on modes of action and adverse outcome pathways.
- **Model-based meta-analysis (MBMA)**—Proprietary, curated databases of publicly-available trial information are used to develop models that compare a drug's effectiveness against competitor products, optimize clinical trials, scale from biomarker to endpoint, and inform marketing decisions.
- **Strategic regulatory writing and communications**—A rigorous, quality-driven process of regulatory documentation and communications support is employed from discovery through life-cycle management.

You should now have a better understanding of what gap analysis is and how it can benefit your drug program. ■

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How to Maximize Submission Quality and Minimize Tears

Does the thought of developing a submission for the marketing approval of a new drug fill you with dread? How do you avoid losing all of your holidays and weekends when developing a submission? Or burning out your team? At Certara, we support teams to develop robust submissions with minimal disruption to people's lives and minimal stress. It's not a fairy tale! It is achievable. But it does require a lot of work, especially upfront.

Moreover, integrating a well-constructed regulatory submission strategy into a sponsor's operational program is even more critical to achieving success than in the past. Between the escalating competition, speed, cost, and risk-benefit pressures on sponsors; the need for payers to see "best-in-value" data of a drug to justify adding it to the formulary; new global regulatory expectations for electronic submissions; or the complexity of the drug itself—strategy is key.

The blog posts in this section address best practices for developing a regulatory writing strategy and preparing your submission to conform to eCTD standards. Read them to learn how we can help you have a smooth submission process that both places your drug in the best light for regulatory bodies and reduces the stress and chaos that so many associate with submissions.

Best Practices for a Successful eCTD Submission

Rob Connelly

The eCTD struggle is real.

Regulatory submissions must conform to the electronic common technical document (eCTD) format to be successfully received and reviewed by health authorities. And while this might seem simple, this complex technical process is actually rife with risk if you lack expertise in medical writing and regulatory publishing.

In this blog post, I'll discuss common pitfalls sponsors encounter in the drug submission process and some best practices for addressing them.

A brief history of the eCTD

The concept of the eCTD was developed by the International Conference for Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group. This working group is an international organization that develops international standards (ISOs).

Their idea was that the CTD (eventually eCTD) could be implemented by every health authority globally to streamline regulatory review of new drugs, and potentially all regulated products. The eCTD contains 5 modules: 1) administrative information and prescribing information; 2) common technical document summaries; 3) quality; 4) non-clinical study reports; 5) clinical study reports.

Modules 2–5 are the common modules of the eCTD. The idea was that once a sponsor developed the content for modules 2–5, they could reuse it for submissions wherever eCTD is accepted: the US, Canada, the EU, etc.

A cautionary tale

Recently, I met with a prospect to discuss how we could help them prepare a submission. This organization's drug candidate is in Phase 3 trials and has received significant venture capital investment. The staff consisted of experienced scientists from academia. So, their experience was really in disease research, and they didn't spend a lot of time focusing on eCTD.

For them, getting documents into an eCTD format using templates was a challenge. Their staff was writing reports without following the eCTD format. And they also weren't collecting the data from studies to conform to eCTD requirements.

By not having their submission conform to eCTD standards, this sponsor could risk a delay in submission which would lead to a delay in approval. This obviously puts pressure on financing the business, treating patients, and maximizing patent length. Also, receiving a "refusal to file" (RTF) from the FDA adds to the time and cost of developing a drug by delaying its review. The submission has *failed,* sometimes within just minutes of arriving at the agency.

RTFs: How they happen and how to mitigate your risk

Here are two common regulatory pitfalls that can invoke an RTF.

- **The submission fails based on *technical errors***—When the FDA receives a submission, they run it through a GlobalSubmit Validate tool. If the submission has serious validation errors (High Errors), they will reject it immediately. For example, the folder structures, files, or XMLs don't meet the validation criteria.
- **The submission fails based on *content***—For example, you didn't include case report forms. Or the data is not in CDISC format. Or you forgot to include an integrated safety summary report, which summarizes all the safety information in the submission.

During the transition period from paper submissions to eCTD, the agency issued many RTFs as sponsors learned how to implement processes for complying with this regulation. And it still happens today.

Ensuring high quality submissions

By embracing regulatory operations best practices, sponsors can avoid the risks of failing to meet eCTD standards and thus incurring an RTF from the agency.

First, we can help from a regulatory writing standpoint by supporting project management and medical writing of the necessary studies. Once the medical writing is complete and the documents are prepared for the eCTD submission, our publishing services team can manage the project from a submissions standpoint. This means that they add the needed reports to the eCTD publishing software and ensure that the submission is valid and will be accepted by the agency the *first time.*

Satisfying regional requirements

You may be thinking to yourself, "OK, eCTD modules 2–5 are common. I just have to get them right, and I'm set!"

Not so fast.

eCTD requirements differ between regions in two major ways: differences in module 1 content and validation criteria. eCTD module 1 contains regional requirements: the prescribing information, packaging, local government forms (eg, PDUFA user fees in the US). Each region has its own submission specifications and requirements. For example, the European Union can accept submissions using their "centralized procedure," which grants approval to market a drug in all EU countries.

Additionally, each region has their own validation criteria by which they scrutinize submissions for errors. So, every time a country or region updates their validation criteria or local requirements, we update the version of our submission validation software for that specific country or region.

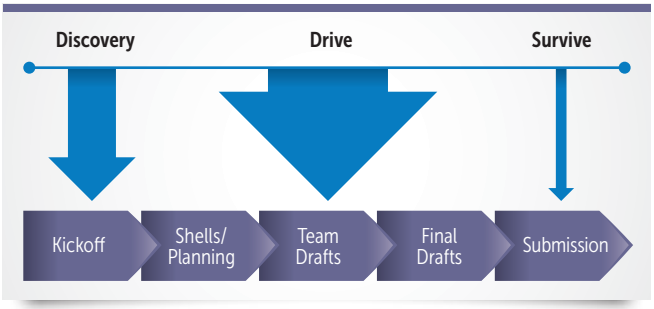
I hope that you now appreciate the complexities involved in developing an eCTD submission. ■

6 Signs You Need Help with Submission Planning

Steve Sibley

Setting and adhering to a timeline for planning, drafting, reviewing, and editing regulatory documents needed for the submission dossier is a major challenge for drug development teams. I think of this process as having three phases: "discovery, drive, and survive." In this blog post, I'll discuss common planning pitfalls and how to avoid them.

1. **Not knowing what "done" looks like**—The experience gained by having been through the entire submission process from development through to defense, approval, and lifecycle management is invaluable. When you're starting a new submission, identify which (if any) team members know what "done" looks like because these individuals will know potential difficulties to watch out for. Ideally, you have an experienced team. If you have a very inexperienced team, look for someone internal or external to your organization who has that experience and can help guide your team through these challenges.
2. **Scheduling summary document preparation in parallel with source document preparation**—This pitfall refers to teams attempting to draft and review either non-clinical or clinical summaries in parallel with the supporting study reports. Trying to keep consistent messaging across documents that are undergoing simultaneous revision is difficult. Although this can be done, it's painful for everyone because this practice creates considerable rework and inefficiency. You'll find it much more efficient for the team to have separated source document prep from summary document prep—and you'll end up with a higher quality final submission with less stress. This is true even if it means shorter review or revision periods for those documents.
3. **Missing input from key stakeholders**—Solicit input from all key groups involved in your submission. Your core team may be limited to representatives from a handful of functions. But you want to include all stakeholders—drug metabolism and pharmacokinetics (DMPK), publishing, and quality assurance. If key people are sitting on the sidelines, try to engage them.
4. **Messaging "cottage industry"**—Creating messaging, such as a target product profile, is essential in drug development. However, be careful that you're developing wording that can be inserted into the summary documents rather than messages created specifically for separate messaging documents. Such wording may not work in submission documents and require that it be reworked to use it in the submission.
5. **Ignoring dependencies**—Make sure that you're addressing dependencies. For example, you can't draft an integrated summary of safety (ISS) until you have the integrated pooled safety output. And that typically depends on getting to database lock on the last phase three study. Account for the time required to get from each submission development step to the next.
6. **Planning for weekend and holiday work**—Don't plan your submission development schedule so that it requires weekend and holiday work. Maintain weekends as weekends and holidays as holidays. Build your schedule so it doesn't require that work. If you build a schedule that requires weekend/holiday work, then that's what will happen.



Creating a detailed timeline

The timeline should include the following information:

- Holidays, vacation or other commitments
- Events or meetings: identify when the team needs to be available for external events
- Document deliverables including drafting, reviews, comment resolution meetings (CRMs), and revisions

By creating a detailed timeline, you can see whether your reviews are staggered or whether they overlap. Or if you have three comment resolution meetings scheduled at the same time. It also helps you identify dependencies so you can make them clear to the team.

Ideally, I will develop the timeline for all documents at least six to nine months before the submission's due date. Once agreed, I also book reviews and comment resolution meetings in people's calendars.

The drive phase

The next and longest phase in preparing a submission is the drive phase. The key here is to maintain your purpose and drive to the submission date. Keep a sense of urgency during this stage. You want to reinforce and build upon the agreements reached upfront. Stick to your timeline and don't let things slip "because there's still time." It's easy to let a review slip one week at this point because it won't impact your submission. But it sets a bad precedent for when you don't have that option of delaying an activity.

During the drive phase, you develop your team's trust with delivery. When the team completes those first few scheduled reviews, comment resolution meetings, other activities, and meets their deadlines, their confidence grows. Having this strong team rapport will be valuable during the more stressful, hectic end of the submission.

Anticipate delays and flaws in the data. You can do that by meeting regularly and documenting the meeting minutes and actions. Don't let outstanding questions linger! The sooner you address them, the better. While meetings are a good way to keep everyone updated, you will also need additional communications between meetings.

If you've ever done a "lessons learned" on a submission, communication was probably identified as an area for improvement. Maybe the communication needed to be more frequent, clear, or widespread. I don't think it's possible to over-communicate on a large submission project. It's more important for everyone to know what's going on than to try to limit awareness of problems. The team must be onboard and know where things stand with the submission at all times.

The survive phase

I call the final phase of a submission the "survive phase." This stage occurs near the end of the project, often right as you need the first document approvals. Every submission reaches a point where things are just going wrong! Submission leaders have to adjust and help show the team the path to success. Provide or find extra support where it's needed.

What happens if you've been following a detailed timeline, and then a problem arises and database lock has to slip a week? *Don't panic.* You have an agreed timeline, so don't change anything that doesn't have to change.

An advantage of developing a detailed timeline is that it facilitates visualizing your options. Maybe you can cut some documents' drafting time if the tables are also delayed by a week. Or perhaps the statistical group can deliver the tables a little earlier. Maybe the team can shave a few days off a study report's review. The inevitable delay arising doesn't need to disrupt the whole timeline. Being able to see the entire submission timeline allows you to minimize the tweaks needed to address issues that arise.

Often, teams find discussing and arriving at an agreement in tough situations difficult. Staying quiet when everyone seems to be working well together is a tempting choice. But team leads who foresee looming problems must address and resolve them because otherwise the submission (and the team) will falter.

"Simultaneous" global submissions

The plan for creating submissions for different health authorities should be baked into your detailed timelines. Discuss how to manage different global submissions at the kickoff meeting, not when you complete the first submission!

Sponsors commonly submit applications for regulatory approval in multiple geographic regions. Pulling this off requires heeding several considerations. Where are you planning to submit the marketing application? In how many different regions or countries? Which ones and when? Filing a submission in the US and Europe simultaneously poses different issues for the team than submitting to the FDA first and then three months later to Europe. This is because you start running into issues of cutoff dates for ongoing studies, changes in safety reporting, etc.

Submitting marketing applications to multiple countries frequently means altering how you write regulatory documents. The indications may have to be changed because of differences in standard of care or wording that the regulatory authority has for that indication. Likewise, the dosage form or dosing strategy may differ between regions. There is also variability in risk management requirements, especially between the US and Europe. Lastly, the disease description may vary in different regions of the world.

Take home messages

All submissions have discovery, drive, and survive phases. In the discovery phase, do your homework! Ask questions to dig into the strengths and weaknesses of the program, its history, submission process aspects, the drug, and disease and indication. Have your submission kickoff 9 to 18 months before the submission date, and create detailed plans that you then make transparent to the team.

During the drive phase, meet regularly with the team, document minutes from those meetings, and follow up on those actions. These habits will help you hold team members accountable. Communicate relentlessly to keep everybody informed.

In the survive phase, submission leaders should be the "calm in the storm." Don't be afraid to speak up, especially when the worst happens, to help drive the team forward.

Many pharma companies put emphasis on "lessons learned" after a submission is completed. Ideally, you will gather these on an ongoing basis and then finalize them immediately after the submission is complete. Document any recommendations that the team would make for future submission teams. To maximize the benefit of lessons learned, a team member should present them at the kickoff meeting for the *next* submission. If the next project has an inexperienced team, having someone present the lessons learned from the last submission will help them have a good start.

By following these recommendations, you are more likely to develop your submission on time *without* losing all your holidays and weekends. ■

Things About eCTD You May Not Have Known

Rob Connelly

In helping clients with their regulatory operations and electronic publishing needs, I'm often asked about preparing regulatory submissions in the electronic common technical document (eCTD) format. While a lot of us have been working in the eCTD format for many years, new start-up companies focusing on rare diseases and new technologies to treat patients are often surprised by the regulatory hurdles that eCTD presents. In this blog post, I'll share answers to some of the most common questions from these clients.

Q: What is the process for getting a submission into the eCTD format, and when should we start?

A: The submission of a marketing application is seen as a key milestone in a long development process. People unfamiliar with the regulations, specifically eCTD requirements, can be caught off guard as their NDA submission date approaches. The NDA medical writers and Regulatory Affairs leads have not prepared their documents for the eCTD publishing stage, and now they realize that documents need to be rewritten to match eCTD granularity and hyperlinking requirements. So, let's first take a high level look at the eCTD which contains 5 modules: 1) administrative information and prescribing information; 2) common technical document summaries; 3) quality; 4) non-clinical study reports; 5) clinical study reports.

The first step is to get your submission documentation into the format specified by eCTD templates. Regulatory and medical writing teams usually write all the clinical and non-clinical studies in content templates that format everything according to eCTD regulations. These eCTD authoring templates should be used for any report planned for a regulatory filing no matter how far off the submission may be.

Once the documentation is in the correct format, the content should be approved by subject matter experts as well as regulatory operations. Once approved, it's transferred to the publishing team who starts the submission compilation. This involves creating PDF files, adding navigation aids (bookmarks and hypertext links), and uploading it to the online eCTD publishing software. Once the publishing team has performed their process, the eCTD files and sections should be reviewed again by the subject matter experts.

Q: What's the XML backbone and how do we create it?

A: The publishing software completes two major tasks automatically. First, it creates the proper folder and subfolder structure that organizes the eCTD documents by modules. It also auto-generates an XML backbone.

The XML allows the eCTD viewing software to load the application and structure the files in their proper order over the life-cycle. The XML backbone provides required metadata as well as document life-cycle operators, which are loaded into the eCTD viewing tool.

Without an XML backbone, your submission will fail the regulatory agency's validation software. Thus, the health agency reviewers will not review your submission because it won't load into the review software.

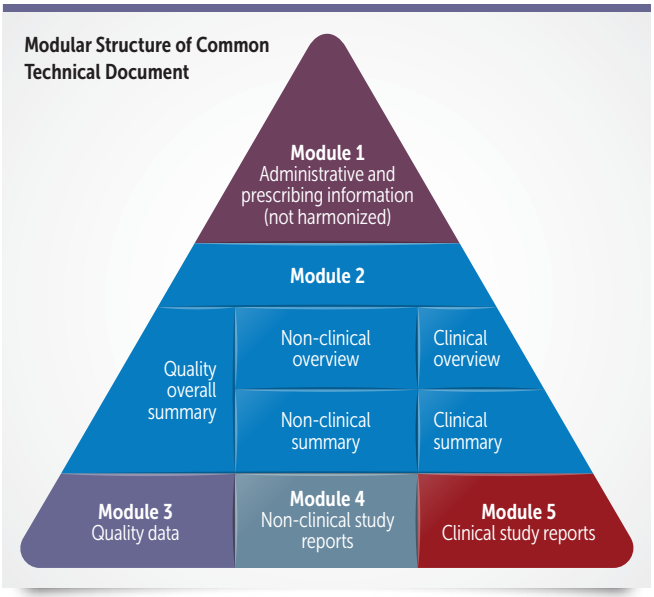
Q: What do people mean when they refer to the "metadata" of a submission?

A: Metadata in the case of eCTD submissions refers to structured data.

Think about unstructured data as a PDF file or a Word document. Large submissions contain thousands of documents with unstructured data.

The eCTD message that is sent contains structured data as well. Some of the information that is entered as metadata with submissions includes the application types, sequence types, sequence numbers, Dun & Bradstreet Number, the regulatory contact name, and their phone number. The regulatory operations will add this information through the eCTD publishing software.

The role of metadata will likely be expanded with future versions of eCTD as eCTD v4 is implemented and potentially impacts identification of medicinal products (IDMP) on Structured Product Labeling (SPL).



I hope that you now know more about the structure of an eCTD submission. ■

Insights from Clinical Transparency and Disclosure Experts

As the issue of transparency and disclosure (T&D) of clinical trial information grows in importance, so has the recognition that sharing clinical trial information is critical to increasing trust between the public and the industry. More importantly, increased transparency regarding ongoing research could spur new products or therapeutic approaches, widen the participation of subjects, and potentially avoid unnecessary trials.

In this section, the blog posts cover two major T&D initiatives within the pharmaceutical industry: disclosure of clinical trial data and writing plain language summaries for clinical trial participants.

A key concern in disclosing clinical trial data is protecting patient and other confidential information contained within those documents. The Synchrogenix CRMS solution is the only artificial intelligence (AI)-enabled redaction solution to automatically identify and redact protected personal data (PPD) and company confidential information (CCI) with more than 99% accuracy.

According to the Institute of Medicine, nearly half of American adults have difficulty understanding and acting upon health information. To address this challenge, Synchrogenix, a Certara company, has partnered with the Center for Information and Study on Clinical Research Participation (CISCRP) to offer plain language communications services.

Read these blog posts to learn how to leverage our technology and regulatory writing expertise to streamline compliance with these T&D initiatives.

Streamline Your Approach to EMA Policy 0070

Lora Killian

Policy 0070—published by the European Medical Agency (EMA) in October 2014—has made the world of regulatory writing a more complicated place. The policy requires specified submission documents to be made public for all marketing authorization applications (MAAs) submitted as of January 1, 2015, and for all indication extensions and line extensions submitted as of July 1, 2015. The Policy 0070 document primarily addresses company confidential information (CCI) rather than personal protected data (PPD). The EMA published the "External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use" in March 2016; this document details policy execution. It specifies additional requirements around PPD. And then in December of 2016, the EMA issued an updated version of the Guidance, with a few significant changes. In this blog post, I'll discuss the complexities created by Policy 0070 and suggest some solutions to manage those challenges.

Deliverables required by EMA Policy 0070

Policy 0070 is a two-round process. In the first round, the "Redacted Proposal Version," the deliverables include:

- A cover letter with templated language provided in the guidance document
- A document list of all the components submitted in the redacted proposal version
- The submission documents that include proposed anonymization changes and proposed company confidential information redactions
- The justification table listing the CCI proposed for redaction
- The anonymization report outlining the method by which the submission documents were anonymized

The second round includes a slightly shorter list of deliverables that will be made public. This list includes:

- The cover letter
- The document list
- The previously listed submission documents with finalized anonymization techniques.
- The anonymization report

Understanding anonymization

What is involved in anonymizing submission documents? Submission documents contain personal data, which the EMA defines as "any information relating to an identified or identifiable natural person ('data subject')." Recital 26 of the EU General Data Protection Regulation which drives privacy handling states, "To anonymize any data, the data must be stripped of sufficient elements such that the data subject can no longer be identified by all likely and reasonable means."

Sponsors must ensure that re-identification cannot occur using linkability, singling out, or inference. Previously, we thought that just removing basic information like clinical trial ID numbers or names from medical records could prevent re-identification of individuals. Through malicious attacks and through demonstration attacks by researchers, we now understand that more must be done to protect privacy. The more information provided about an individual (not including names), the easier it is to re-identify someone using the information in the document and outside sources. Preventing re-identification is difficult and impacts data utility. So, the EMA requires sponsors to assess the re-identification risk of their anonymization methods.

The options to anonymize documents include:

- Masking—otherwise known as redaction—obscures personal data with black boxes, or in the case of the EMA, blue boxes.
- Other techniques, which include:
  - Noise addition
  - Permutation
  - Differential privacy
  - Aggregation
  - K-anonymity
  - L-diversity

These options have different impacts on the risk of re-identification and data utility.

Why redaction is the dominant anonymization technique (for now)

Currently, most sponsors prefer using redaction. The first six Policy 0070 documents made public at different times since October 20 by the EMA used redaction techniques. The EMA acknowledged in the Guidance that this would be the industry's preferred route in the initial implementation of Policy 0070.

Redaction is appealing for several reasons. First, we are dealing with retrospective redaction. Many trials in the submissions currently being prepared for Policy 0070 and some of the clinical study reports written for those trials were prepared before Policy 0070 was published. Thus, patients who participated in these trials were not informed that their information was going to be made public, the documents

were not written with publication in mind, and contracts with study administrators were not written with publication in mind. Likewise, some of the other techniques require reverting from PDFs to Microsoft Word documents to modify content. Re-opening documents for modification has quality control and cost implications.

Who is entitled to privacy under Policy 0070?

PPD in regulatory documents typically covers the following groups:

- Patients plus spouses, partners, or children referred to in studies
- Study administrators including investigators, sponsor employees, committee members, and vendors

What goes into the anonymization report?

The anonymization report outlines how the sponsor anonymized the documents. Additionally, sponsors must explain how they maximized data utility. The EMA has suggested that they will not review the submission documents for all proposed anonymization; they will review the anonymization report and provide feedback on it. We have learned that in these early phases the EMA is reviewing the anonymization report and the proposed anonymized documents.

Keeping CCI under wraps

CCI is information not in the public domain and where disclosure may undermine the sponsor's legitimate economic interest. Sponsors must list all proposed CCI redactions in the justification table. This table must also include the location of the CCI and the rationale for requesting its removal. During the consultation phase, the EMA will both validate what has been proposed for removal and provide feedback on CCI in the justification table.

Transparency and disclosure prior to Policy 0070

Prior to Policy 0070, most transparency efforts made by sponsors were a result of EMA Policy 0043, sponsors' own transparency policies, and clinical study report (CSR) documents submitted with publications. Under the sponsor's own transparency policies, the sponsor had complete control over how to anonymize their documents for publication.

Under Policy 0043, some sponsor transparency resulted from individuals (typically researchers but often competitors) requesting documents from the EMA or directly from sponsors. In the case of Policy 0043, EMA typically redacts the documents and allows sponsors to suggest additional redactions or modifications to existing redactions proposed by the EMA. For requests made directly to sponsors, the sponsor chose what and how to anonymize. In both cases, the documents were provided to individuals. And in the case of direct requests, the sponsor could determine the terms of use.

The brave new post-Policy 0070 world

In this post-Policy 0070 era, the practices are different. Rather than establishing overall anonymization policies, sponsors must assess every submission to determine unique anonymization techniques that will maximize data utility and protect patient privacy. Sponsors can no longer have complete control over how to anonymize their documents. The EMA is weighing in on how anonymization should be performed.

Moreover, Policy 0070 has created additional deliverable requirements: the justification table and the anonymization report. Unlike Policy 0043 documents, the Policy 0070 documents are being made public, not going to an individual. Lastly, the EMA dictates the terms of use for individuals accessing these publicly posted documents.

The timeline for submissions under Policy 0070

The EMA has proposed the following submission process under Policy 0070. The redaction proposal versions are to be supplied to the EMA between 181–220 days after submission. The consultation phase is supposed to take around 42 days. Sponsors will then have 27 days to implement and respond to the EMA's feedback. Finally, the documents will be published within 60 days of the European Commission issuing its decision.

But, we are not there yet. Currently, the EMA is playing catch-up. They are working back from the earliest opinions in September of 2015. Based on our clients' experiences, the EMA requests that the redacted proposal version be provided within 30 days, but this deadline appears to be negotiable. The sponsor delivers the redacted proposal version at the agreed upon date. For now, sponsors are taking several months to get through consultation. Obviously, the EMA is aiming to expedite this portion of the process. Once the consultation is complete, the final redacted version is submitted to the EMA with the agreed upon updates.

Developing a rule set for your redaction policy

With the anonymization technique of redaction, sponsors must determine the rules that will govern their redaction policy. Then, they must apply these rules across the documents and explain them in the anonymization report. In the pre-Policy 0070 days, one fairly conservative rule set could be applied across all trials. That is no longer the case in the Policy 0070 era. Different rule sets are needed for different trial types. The characteristics driving the different rule sets we have created for sponsors include:

- Disease prevalence
- Population size
- Number of study sites
- Number of patients per site
- Sites per country

Who approves these rules for each sponsor? A group of stakeholders participates in transparency and disclosure decisions, particularly around Policy 0070 because of the broad publication of the documents. The stakeholders typically include representatives from:

- Medical writing because they are closest to the sponsor's documents
- Statistics because they typically have experience preparing de-identified data sets
- Legal because they represent the sponsor's privacy policy

- Regulatory because they communicate with the EMA
- Therapeutic area representatives because they know the particular compound, can represent the complexities of the submission, and understand what should be considered CCI

Why is Policy 0070 compliance so complex?

Many steps are required to prepare a Policy 0070 submission. What makes its requirements so complex? Here are some areas for consideration.

What has the sponsor posted on ClinicalTrials.gov? Sponsors provide investigator information, including location, on ClinicalTrials.gov to aid recruitment. It lets the public know if the trial is taking place locally and provides volunteering information. However, what if this trial is a rare disease study or small population in which at a later date, under Policy 0070, the sponsor wants to redact investigator information to provide greater anonymization for patients? In small studies with small patient populations, investigator location information and even investigator identities can be a proxy for patient location. Providing patient location increases the risk of patient re-identification.

Another complexity is around scope. In the initial version of the Guidance document, only trials provided in submissions made after January 1, 2015, needed to have their corresponding CSRs included in the submission. However, in the updated Guidance published in December of 2016, any trials referenced within a submission might be considered in-scope for the purpose of Policy 0070. This becomes a significant issue for pediatric submissions. In the EMA, CSRs for pediatric studies must be delivered within six months of trial close. For a pediatric submission made after January 1, 2015, all the corresponding studies may have been provided separately prior to that date. Per the updated Guidance, those trials are now in scope.

For other submissions, such as line extensions or indication extensions, the "cross-referenced" studies within the submission may not be clearly in-scope for this new rule, causing confusion and potential delays in preparing a Policy 0070 submission in advance of the deadline.

Study characteristics also pose issues. Many of the sponsors we support in Policy 0070 preparation have chosen to redact gender for patient information. What happens when a trial is one gender and that gender has already been posted on ClinicalTrials.gov during the registration process?

Some of the sponsors with whom we work have also chosen to redact race and ethnicity. Similar to the gender scenario, what happens when a study is conducted in a single race and that race is posted on ClinicalTrials.gov? Should a sponsor attempt to redact it from documents if the information is already in the public domain? Should sponsors make earlier efforts to keep this information confidential both for the registration process as well as the publication of the document?

Policy 0070 and redaction

Redaction is more complicated under Policy 0070. The redaction complications concern the following:

- Sections within the document: what do you do with listings, narratives, mini-narratives for non-standard trials?
- Demographic complications like the issues we proposed with single gender or single ethnicity studies
- Other identifier type complications: for non-standard studies, does the medical information create too high a risk of re-identification; if that information is removed, does any data utility remain?

Creating the anonymization report and justification table

Developing the anonymization report is complicated. First, sponsors must choose either a qualitative or quantitative method to assess the risk of re-identification for each submission. Sponsors must then establish their desired risk threshold. Corresponding with this decision, they must next assess the likelihood of different attacker scenarios. Sponsors must then assess the risk of re-identification against the pre-determined threshold. They must also justify how data utility was maintained. Lastly, sponsors must make global redaction decisions as well as decisions specific to each submission and, potentially, each trial.

The justification table complications concern the fact that each proposed CCI redaction requires a unique rationale. The EMA does not accept "canned answers" for CCI requests.

Learn more about streamlining document redaction

Over time, many of these complexities will resolve. Sponsors will gain experience, incorporate best practices into writing these documents, and have access to technologies that handle the complexities in a more sophisticated manner. We are innovating to bring sponsors greater options to address their transparency and disclosure needs.

Our partnership with PleaseTech is part of our innovation strategy. PleaseTech's newly announced PleaseReview's 6.0 software release provides users with redaction capabilities. While the complexities remain today, PleaseTech's future 6.1 release of PleaseReview will enable Synchrogenix to create a seamless redaction process that streamlines collaboration in the Policy 0070 era. ■

Avoiding Pitfalls in Plain Language Summaries of Clinical Trial Results

Behtash Bahador

Building trust with clinical trial participants is critical to the success of drug development programs. One of the best ways to earn that trust is by meeting their expectations regarding learning study results. In fact, a 2015 study by the Center for Information and Study of Clinical Research Participation (CISCRP) showed that 73% of clinical trial participants want a summary of their study results (the plain language summary). That same study also indicated that receiving these results helps meet participant expectations which in turn increases their likelihood of sharing their trial experiences. This positive cycle of patient engagement increases trust in research and interest in future participation.

However, the current transparency and regulatory environment creates an unintended dichotomous view that pits meeting patient needs against satisfying transparency and regulatory requirements. In this blog post, I'll discuss a model that balances these seemingly competing interests.

The current regulatory environment for plain language summaries

Both the European Union (EU) and the United States have issued regulations regarding plain language summaries. The EU Clinical Trials Regulation, which will become effective in 2019, requires a layperson summary for all Phase 2–4 interventional trials. Sponsors must post these summaries to the EU portal within 12 months of the end of the clinical trial. A lay summary is required in each of the local languages where the trial occurred in the European Union.

In the United States, the final rule on clinical trial registration and results information submission does not require submitting technical or non-technical summaries. The rationale was concern regarding ensuring that the summaries would be consistently objective and non-promotional. However, they have acknowledged that industry efforts to return results to participants may be informative to the department of Health and Human Services. And, they will review these efforts to evaluate the feasibility of requiring plain language summaries.

Demonstrate a commitment to patients, not just meeting regulatory requirements

Programs providing lay language summaries of trial results have typically been designed to meet the needs of the volunteers that participated in the study who want and deserve to learn these results. Yet, the draft guidance from the EU on the development of summaries clearly states, "Develop the summary for a general public audience." This complicates the task for summary creators.

Principles of health communication tell us to *know and engage the target audience.* With the introduction of the EU Regulation, we now must write for both members of the general public with no prior knowledge of a trial while also creating a plain language summary that satisfies the needs of trial participants. One challenge we face is the need to convey appreciation to study participants. This is one of the most important elements of communicating with patients. But, how can we engage participants with this message when the summary is written for a general public audience?

Additionally, user testing of our lay summary template revealed the need for a section about the study design and schedule. This information helps engage readers to ensure better understanding of clinical trial designs. For study participants, this information reminds them of study procedures which took place a year or more prior. Importantly, this also provides a base of knowledge which aids in understanding trial results. Yet, this information is not explicitly required by the EU's lay summary template, which is meant for someone without prior knowledge of the trial.

Another challenge is the need for complete reporting of information to avoid perceptions of withholding important findings while also sharing only the most scientifically supported results to avoid misinterpretation of the validity or applicability outside of the context of a single trial. In a summary intended for lay audiences, this must also be done as succinctly as possible. Unfortunately, omitting information that could be of interest to patients or the general public is often justified with the rationale that a link to the full results is provided. This attitude contravenes the tenets of health communication. The full trial's results are *technical.* They're nearly impossible for lay audiences to understand. Thus, linking to full results is a strategy that must be carefully utilized; it is not a catch-all.

Given all of these concerns, summary creators strictly following the EU requirements and guidance can miss the mark both on engaging readers and effectively achieving understanding of the trial results. The visual presentation of the lay summary (ie, design and formatting) is an important element that adds engagement and educational value, but there is no mention of this in the aforementioned EU guidance. The best way to ensure a lay language summary meets these critical goals is to involve patients and patient advocates in the development process. While available guidance indicates this best practice in health communication can be implemented during template development, each and every lay summary produced by CISCRP in coordination with Synchrogenix is reviewed by these essential stakeholders. It is not only feasible to do this, but it is a requirement from the perspective of

advocates and even sponsors. Producing non-promotional and easy-to-understand summaries of trial results can only be accomplished through a process that addresses the challenges noted above and the many more that arise with each development project.

Writing lay language trial results summaries

Using patient-friendly language is becoming more and more of a priority for us. A challenge of writing plain language summaries is how to write in this language and also stay true to the scientific basis of a study.

We have to balance what is interesting to patients and what is interesting to scientists. Patients want to know whether a drug is a safe and effective treatment for their disease. In general, they want "black and white" answers.

Researchers want to explain the results of clinical trials in a precise and often nuanced way. They aren't comfortable making "black and white" conclusions. Their conclusions contain many caveats: we tested this drug in a particular setting with a specific population. It *may* be safe and effective in these conditions. And a "shades of grey" conclusion is unsatisfying to the patient.

Can we write statements that would be more satisfying to patients? For instance, "this new treatment is better than the standard of care" or "this treatment ameliorated the disease symptoms?"

These statements address the patient's interests. However, they are promotional and, frequently, inaccurate. This is because an approved drug's label claims are not just based on one trial. They are based on evidence collected across multiple trials. So, we can't provide patients with "black and white" trial results.

Compounding this challenge is scientists' use of technical language to describe drug development. Pharmacokinetics. Antibody. Crossover study design. This technical language is incomprehensible to the general public. How do we develop a scientifically valid, plain language translation of a study that satisfies both the scientist and the patient?

Writing to communicate with a lay audience

One idea is to keep the language understandable to a lay audience by writing to the 6th–8th grade level. Therein lies another challenge! The information that is considered "6th–8th grade" varies greatly even between schools in the same district.

Both the NIH and EU provide guidelines on writing using plain language. Some non-governmental groups like TransCelerate also provide guidelines regarding health literacy principles. While these tools help us to understand the spirit of what that middle ground looks like, none of them are an absolute solution.

For example, both the CDC and the University of Michigan provide glossaries of plain language terms. But there is no standardization in this field. Thus, different plain language suggestions can be provided for the same scientific term. So, to discuss "interventions," do you use the CDC's recommended terms ("action, treatment, or program") or the University of Michigan's ("care")?

Readability metrics

Say you've used these guidelines and glossaries to write a plain language summary. How do you know that a patient will actually understand it? Many people rely on readability metrics. The Flesch-Kincaid—based on word and sentence length—is most frequently referred to in this space. But, using readability metrics also poses challenges.

For example, using longer words and sentences is sometimes necessary. "Fever" is a concise lay substitution for "pyrexia." But, what if your study involved a drug for respiratory syncytial virus? In this case, a longer explanation ("a virus in the airways that can cause pneumonia") is the clearest.

The iterative process of writing lay summaries

Sponsors often struggle to write these documents. The first struggle involves scaling up their plain language summaries program to satisfy new requirements. To address this challenge, the clinical operations team often creates a master template that incorporates the regulatory requirements into the summary.

However, this isn't an ideal solution because each team wants to write the summaries using their own specific language. Thus, to achieve scalability, we recommend educating study teams about plain language writing, not using templates. Create ownership expectations with the group that is authoring the summaries.

Consistency is also critical. You need to present patients with the same messaging from study to study. To do this, seek agreement on therapeutic area language, study design approach, etc. Creating messaging consistency makes lay summaries easier for patients to understand.

Telling the story of a clinical trial

It's human nature to want to tell stories with a clear narrative arc. But, sometimes the desire to tell a compelling story can skew the balance.

For example, a company was doing a safety and pharmacokinetics (PK) trial in a specific disease. As they were conducting the trial, they found interim exploratory results suggesting the drug was effective. The team writing this trial's lay summary wanted to stress these efficacy findings because they felt that this information would interest patients. However, the trial's primary outcomes were for safety and PK. So creating that kind of patient communication becomes promotional as the efficacy claims wouldn't have adequate statistical power.

Our best practice is to use regulated documents, such as clinical study reports (CSRs), as the source for plain language summaries. This ensures that the results we share with patients agree with the intent and design of the study. Moreover, we work with sponsor teams to set expectations as to the regulatory requirements for summaries.

Including the patient's voice in regulatory documentation

We have an ethical imperative to consider the patient's perspective in designing studies. Consider this scenario: Company X writes an informed consent form (ICF) that includes potential biomarker analysis of additional patient blood draws.

From the patient's perspective, they're getting pricked many times. But these biomarker blood draws aren't part of the study's objectives, so they're not reflected in the CSR. Thus, we don't write about these blood draws in the patient summary and assume that the patients won't wonder what all those needle sticks were for. That's a dilemma because this is a big part of the trial from a patient's perspective. We have to continue communicating the purpose of the trial and provide clarity around what happens to the patients.

We must include the patient's voice throughout the clinical study process. Starting with the study design, are we performing only the necessary assessments? Are we using technology like modeling and simulation to minimize blood draws? Can we avoid certain clinical trials completely, for example, using physiologically-based pharmacokinetic modeling to explore drug-drug interactions?

An overview of our recommended process

At CISCRP and Synchrogenix, we have established a process for our lay language summary programs. We start by setting expectations with the informed consent document, which informs the participants that they will receive the results of the clinical trial in an understandable format. CISCRP research has shown that 52% of patients said it's very important to know if summary results will be provided before deciding to enroll in a trial. As the first touch point with participants, the ICF provides an opportunity to demonstrate your commitment to meeting patient needs. Next, CISCRP provides a "thank you" communication as participants leave the trial to remind them that they will receive the results and thank them for their role in advancing medical science.

For longer trials, we also provide brief communications once or twice annually to update participants on the availability of results. These communications are printed and sent to the investigative sites who then pass it on to their patients. Investigative sites appreciate this opportunity to strengthen their relationship with their patients.

We also use these communications to provide general education about the research process. The end of the process is providing the lay language summary to participants either in a printed format delivered to study sites or posted electronically to an online portal.

Through the Synchrogenix-CISCRP partnership, we've developed a stable, transparent, and reliable process for developing plain language summaries. ■

How AI Tech Is Changing Regulatory Writing

Nirpal Virdee

Did you know that you're likely using artificial intelligence (AI) in your everyday life?

For example, the digital music service, Spotify, creates "mood-based" playlists that are curated to users' musical preferences. Spotify generates these customized playlists using a machine-learning algorithm that has learned your unique musical preferences based on your previous interactions with songs, musicians, and playlists.

AI technology is driving innovation for multiple industries, including pharma. In this blog post, I'll discuss how using AI for regulatory writing is reshaping drug development.

The ROI on AI technology

The timeline for launching a drug to market typically involves a decade of discovery and pre-clinical research followed by another eight years for clinical trials. AI could streamline that process dramatically by cutting time and costs spent on clinical trials. In this respect, investing in AI technology could yield a significant return on investment (ROI).

AI: from skepticism to enthusiasm

Until recently, pharmaceutical companies employed structured authoring to streamline document writing. Structured authoring defines the structure of a document and what content should go in each section.

But all the money and time invested in structured authoring hasn't provided a sustainable solution because of the industry trend towards mergers and acquisitions. Each time one company acquires another, you end up with reports in many different formats. The resulting document heterogeneity wipes out any efficiency that structured authoring provides.

Currently, the main uses of AI are in basic drug development research. But there is a renewed desire to use these advances in late stage development.

With the use of AI machine learning in helping us write regulatory documents to smart objects that redact sensitive data for publication, we are moving from relying on structured content and methods to contextual-based understanding. These techniques will only get more sophisticated from smart, rule-based objects to learning objects that can adjust approaches and interpretation. So instead of using AI-configured smart objects to develop specific clinical reports, we will move towards the sole use of learning objects that automatically interpret the type of input data to develop the appropriate output reports. It won't matter if we insert a SAS dataset for narrative generation, protocol and SAP for clinical report writing, or full clinical study report (CSR) and submission documents. AI will interpret the input and self-generate full narratives, complete study reports, or a redacted set of reports for publication.

Our capabilities to merge structured and unstructured data and the ability to use datasets, reports, and external sources to seamlessly cross check or enhance your internal analysis will revolutionize clinical development. The benefits of this approach include smarter data interpretation, faster data manipulation, and more efficient and cost effective generation of the outputs needed to support getting drugs to market.

AI crunches research time

Unlike humans, AI can process huge amounts of data and find and manipulate valuable information. It can interpret contextual information and use natural language processing to combine phrases and statements to understand user's commands or self-interpreted decision trees. This ability combined with business and writing rules enables AI tech to generate draft regulatory writing documents.

We started using AI for CSR writing. CSRs are enormous reports that comprise part of the submission package. Writing these documents is labor-intensive and tedious. Much of the effort in writing a CSR involves identifying information in previous study documents and putting it in the right tense.

These mundane activities don't utilize the scientific knowledge and talent of your medical writing team. AI technology can expedite CSR writing by taking information from previously authored study documents (the trial protocol; the statistical analysis plan; and tables, listings and figures) and putting it into the right places in the CSR. Like a person, AI understands the context of information in study documents and interprets where it belongs in each study report section. Our AI system also evaluates data in tables to create fact-based, non-interpretive results text. Using this technology can automate up to 80 percent of time spent writing CSRs. Now, the medical writers are freed to focus on the parts of the CSR that require higher level scientific interpretation.

The purpose of AI is to aid medical writers, not to replace them. Without AI technology, you could spend weeks just generating the CSR draft. AI tech can generate a draft report in 24 to 48 hours. Then, the writers only have to complete the final 10 to 20 percent of effort. This time savings can help your submission be the first to market.

Accelerating your marketing authorization ultimately impacts how much potential revenue an asset can generate.

Using AI to support transparency and disclosure activities

In addition to expediting document writing, AI technology is also being leveraged for redacting sensitive information from clinical trial documents. This application is booming with the emergence of EMA Policy 0070. Every pharmaceutical company submitting to the EU must comply with this requirement to publish CSRs and summary reports while ensuring that they don't risk re-identifying any patients or study administrators. Sponsors must accurately and consistently redact personal protected data (PPD) from these documents.

And that's where AI technology provides tremendous value. This technology understands the context of the sensitive information in clinical documents as well as business rules to identify and redact PPD as well as support the process to redact company confidential information (CCI).

AI also provides greater accuracy and consistency than manual approaches. When it comes to protecting patients' privacy, *good is just not good enough.* The liability of accidentally exposing even one patient is huge.

Unlike conventional manual approaches, using AI for redaction is a scalable solution.

When we first started using AI for redaction, sponsors were spending over six months to redact just four documents. Currently, we're working with one sponsor and redacting 50 documents per week. In total, we are redacting hundreds of documents per month across our sponsor base. Achieving that level of productivity and consistency with a manual effort is impossible.

AI tech helps optimize resource allocation

Entire study teams review the data to be redacted from clinical trial documents. For example, medical writers are typically central to the redaction process. However, having highly trained medical writers spend inordinate amounts of time manually removing information from thousands of pages of documents is a poor use of this resource.

Likewise, the legal team often defines CCI. Again, manually identifying CCI is an inefficient use of this high-value resource. The reason you have these high-value resources working on redacting documents is because the impact to the organization is so significant. And that's where AI really provides value: it automates much of these manual processes. Thus, the impact on these resources for achieving compliance with regulations like Policy 0070 is minimized.

Bigger players changing the technology landscape, tools and infrastructure

Over the last few years, the big technology giants have invested heavily in AI. This is exciting news as new tools, techniques, and data infrastructure become more readily available for pharma to use.

Microsoft is currently researching "automated reasoning, adaptation, and the theories and applications of decision-making and learning."

According to CB Insights, Google—the most prominent global AI player—has completed five acquisitions in the space since 2013.

The tech giant, which acquired London-based AI start-up DeepMind in 2014 for £400m, is exploring different aspects of machine learning, including deep learning and neural networks.

Steve Wozniak, Apple's co-founder, acclaimed AI's transformative potential during an innovation summit in Brisbane, Australia. Quoted by the *Sidney Morning Herald,* Wozniak said, "Until recently... artificial intelligence really didn't make much difference in life, but now we're getting to the point where we're getting closer to what the brain is."

He concluded, "I looked at the brain my whole life thinking we would never understand how it's wired, never know what consciousness is, we would never know what intuition is. And now we're seeing so many signs that are getting so close—we speak to our phones, we can get answers."

Amazon became the latest tech giant to give away some of its most sophisticated technology by unveiling DSSTNE, an open-source AI framework that runs its recommendation system.

The news comes after a *Wall Street Journal* report claimed Amazon was "boosting its artificial intelligence chops" last year.

According to the article, Amazon had hired AI developers in Europe and data scientists for its New York and Berlin offices.

Like its peers, Amazon has also made AI-tech acquisitions such as Silicon Valley-based Orbeus, a recognized API focused on visual recognition technology using deep learning.

Watson, IBM's AI computer system famed for beating some of the world's best chess players, can answer questions posed by humans. Developed by IBM's DeepQA research team, the tech giant announced it would use Watson to solve cyber-crime "once and for all."

IBM is now expected to spend next year collaborating with eight universities to teach Watson to detect potential cyber threats.

Learn how AI technology can help you meet T&D mandates

Our regulatory and medical writing AI solution meets the promise of automated authoring documents such as patient narratives. This is also the most effective and efficient approach for meeting data transparency requirements. ■

The Evolving Regulatory Agency and How to Navigate It

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 serve our clients. We have ongoing collaborations with many global health authorities, including the FDA, EMA, PMDA, MHRA, MPA, and ANVISA. As just one example, our Simcyp division has a research agreement—an FDA Cooperative Research and Development Agreement (CRADA)—with their Center for Veterinary Medicine (CVM). And we also help support the ability of regulatory agencies to review submissions. In keeping with our educational mission, we've trained over 400 FDA regulators to use Phoenix, our PK/PD modeling and simulation software.

With the appointment of Dr. Scott Gottlieb as FDA Commissioner last year, the agency's focus is changing under his leadership. Read these blog posts to learn about how the FDA is evolving and what you can do to keep on top of these regulatory trends.

New FDA Commissioner Endorses Use of M&S to Advance Drug Development

Suzanne Minton

With the swearing in of Dr. Scott Gottlieb as Commissioner of Food and Drugs in May, many have wondered as to the climate he will set for the US FDA. Certara's mission and business thesis aligns with the FDA's July 7 announcement regarding the steps it is taking to implement the 21st Century Cures Act. In this announcement, Dr. Gottlieb cited three areas of focus for the agency in the next several years.

1. Leveraging modeling and simulation (M&S) to increase the efficiency of drug development: Quoting Dr. Gottlieb on his view of the role of M&S in drug development:

> *FDA's efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of these state-of-the-art technologies. FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms.*

He also wrote about using of M&S to support precision dosing—providing the right drug dose to maximize therapeutic benefit while reducing risk for each individual patient. The emerging precision dosing field harnesses the explosion of genomic data and various markers of bodily functions using mathematical modeling to ensure that individuals get the best possible treatment.

In addition, he cited CDER's use of M&S to review Investigational New Drugs Applications (INDs) and New Drug Applications (NDAs). M&S can inform clinical management strategies described in drug labels. In particular, physiologically-based pharmacokinetic (PBPK) models can provide insight into drug mechanisms. This approach considers both intrinsic and extrinsic factors. These factors include genotype, disease state, renal/hepatic impairment, ethnicity and age.

PBPK models incorporate information about how drug exposure changes with drug-induced enzymatic inhibition. Thus, the models can predict and quantify the magnitude of potential drug-drug interactions (DDIs). Sometimes, they can even eliminate the need for additional clinical studies. This tool can be used to develop dosing recommendations for special populations—children, pregnant women, and patients with organ impairment—who can be difficult or impossible to be studied via clinical trials.

2. Using natural history databases to support model-based drug development: To make clinical trials more efficient, the agency is looking to model some aspects of the placebo arm of clinical drug trials. This will be especially impactful for rare diseases—defined as diseases affecting less than 1 in 2000 people. Because of small numbers of patients, it is extremely difficult to recruit enough volunteers for inclusion in clinical trials investigating orphan drugs. The FDA is looking to create natural history databases to support these efforts.

Publicly available clinical trial data represent an underutilized source of information. If properly extracted and analyzed, they provide valuable information to support drug development decisions. Based on years of experience exploring and analyzing publicly available data to perform model-based meta-analysis (MBMA) for our clients, we created an extensive collection of analysis-ready Clinical Trial Outcomes Databases. These databases capture high-quality public source data on drug efficacy and safety, drug, trial, and disease characteristics, trial design, and other relevant information to make key development and commercial decisions.

Our 40 databases provide comprehensive up-to-date information on major therapeutic areas such as CNS & Pain, Oncology, Immunology, Metabolic, Infectious Diseases, and more. For easy access, our Collaborate portal can be used to explore the databases through the integrated Clinical Outcomes Database Explorer (CODEx) interface. CODEx enables users to quickly visualize, explore, analyze, and communicate database content using a variety of highly interactive tools.

3. A mandate for patient-centric drug development: The agency also plans to focus on patient-centric drug development. As stated in the Plan for Issuance of Patient-focused Drug Development Guidance:

> *Patients who live with a disease have a direct stake in drug development and in the outcome of the FDA review process for new drugs. Patients are also in a unique position to contribute to an understanding of benefit and risk considerations throughout the medical product development process. Under the 2012 FDASIA reauthorization of the Prescription Drug User Fee Act (PDUFA), FDA pioneered the use of patient focused drug development (PFDD) meetings to help address the need for systematic collection of direct patient input. The twenty-two PFDD meetings we have held so far have each focused on a different disease area and have identified key findings including that patients living with a disease are experts on what it is like to live with the condition. In addition,* ***the meeting highlighted that what patients care most about may not always be factored into clinical trials or approved labeling.***

I'm happy to see the growth in patient-centric drug development because ultimately we are working to bring them safer, more effective medications to improve their quality of life. We have an ethical imperative to consider the patient's perspective in designing clinical studies. Starting with the study design, are we performing only the necessary assessments? Are we using technology like modeling and simulation to minimize blood draws? Are we using patient-friendly language so that clinical trial participants can understand the summary of their study results (the plain language summary)? Synchrogenix, a Certara company, and the non-profit Center for Information and Study of Clinical Research Participation (CISCRP)—an organization dedicated to educating and informing the public and patients about clinical research—have an exclusive partnership to provide lay language clinical trial results to clinical trial volunteers. Through this collaboration, Synchrogenix, Certara's regulatory writing consultancy, significantly increased global medical writing capabilities supporting an initiative that CISCRP pioneered four years ago. This new partnership combines Synchrogenix's technology-enabled operational expertise and clinical writing talents with CISCRP's unbiased governance and dedication to engaging patients and the public in the spirit originally intended of the clinical research process.

While none of us can be certain what the future will bring, I am encouraged by the tone that the new commissioner is setting at the agency. He has endorsed the technology needed to advance the science of drug development while keeping patient's needs at the forefront. The FDA of the 21st century is developing a regulatory climate that helps sponsors expedite getting crucial medicines to the patients who need them most. ■

Modeling and Simulation Take a Prominent Role in FDA's Newly Published DDI Guidances

Ellen Leinfuss

On October 25, 2017, the FDA published two new guidance documents on drug-drug interactions (DDIs). These guidance documents replace the February 2012 guidance, *Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.* According to the FDA, these new guidances reflect the agency's current thinking and greater learnings on DDIs and provides a more systematic and risk-based approach to this critical topic. Additionally, it creates further alignment with other global regulatory agencies, specifically the EMA and Japan's PMDA.

- The first guidance, *In Vitro Metabolism- and Transporter-mediated Drug-drug Interaction Studies* addresses how to extrapolate *in vitro* data to determine if clinical DDI trials are required, and if so, how those data can inform the trials. This decision-making process generally (but not always) occurs early in the drug development process with the potential DDI liability impacting a sponsor's decision to move forward with an investigational drug. This guidance includes considerations when choosing *in vitro* experimental systems, key issues regarding *in vitro* experimental conditions, and more detailed explanations regarding model-based DDI prediction strategies.
- If an *in vitro* assessment as determined from the above guidance suggests that the sponsor should conduct a clinical DDI study, that sponsor should refer to the second new related guidance, *Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications,* which addresses the conduct and interpretation of clinical DDI studies.

Growing Importance of Modeling and Simulation (M&S)

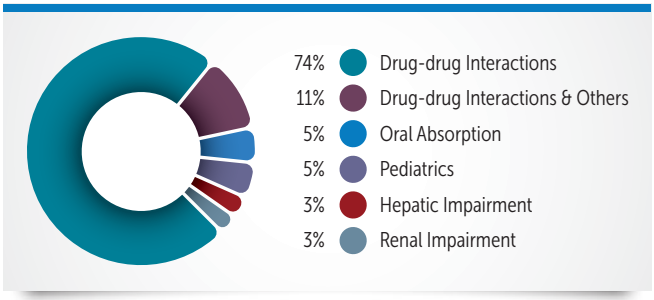
These new guidances demonstrate the FDA's increased confidence in M&S for drug development and review. In a July 7 announcement regarding the steps the agency is taking to implement the 21st Century Cures Act, Commissioner Scott Gottlieb wrote:

Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials.

The endorsement of M&S for informing DDI risk assessment is also seen in these new guidances. The *In Vitro* DDI guidance includes a chapter called "Using Model-based Predictions to Determine a Drug's Potential to Cause DDIs," which outlines a range of M&S approaches to translate *in vitro* observations into *in vivo* predictions of potential clinical DDIs—from basic kinetic models to both static and dynamic mechanistic models that include physiologically-based pharmacokinetic (PBPK) models. In many cases, negative findings from early *in vitro* and clinical studies, in conjunction with model-based predictions, can eliminate the need for additional clinical investigations of a drug's DDI potential. PBPK models can predict the DDI potential of an investigational drug as an enzyme substrate or an enzyme perpetrator. Alternatively, the sponsor can use a PBPK model to inform the need for conducting additional studies.

The new clinical DDI guidance speaks to M&S for both informing DDI clinical trials and replacing the need for trials. The sponsor can simulate various DDI scenarios using available pharmacokinetic models (either mechanistic PBPK models or empirical population pharmacokinetic models) to optimize study sampling (eg, sampling times, number of subjects) and data collection. Population pharmacokinetic analyses of data obtained from large-scale clinical studies can help characterize the clinical impact of known or newly identified interactions and determine recommendations for treatment modifications when the investigational drug is a substrate.

The clinical DDI guidance also outlines how PBPK models can be used in lieu of some prospective DDI studies. For example, PBPK models have predicted the impact of weak and moderate index inhibitors on some CYP2D6 and CYP3A substrates as well as the impact of weak and moderate index inducers on CYP3A substrates. The chart below shows the increasing acceptance of this approach in the FDA's acceptance of PBPK in lieu of clinical trials.



Taken together, these guidances demonstrate the great progress that M&S has made in drug development and regulatory review. Specifically, they clarify the FDA's growing comfort and reliance on these methods. Further, they speak to the future of M&S within regulatory science and ongoing work to advance its use: "PBPK models can include ADME processes mediated by transporters as well as passive diffusion and metabolism. However, compared to CYP enzymes, the predictive performance of PBPK modeling for transporter-based DDIs has not been established." We would say, has not *yet* been established! ■

What the FDA Expects from Your Pediatric Drug Program

Barry Mangum

Historically, 80% of medicines used in children had little to no data guiding prescribers on proper use. To address this market failure, regulatory legislation for drug development in pediatric patients was passed worldwide over the past decade. The number of drugs tested in and labeled for children has increased dramatically as a result. In this blog post, I'll discuss the latest FDA regulations on pediatric drug development.

The FDA's guidance for the pharmaceutical industry

The major pieces of US regulation on developing medications for children are:

- The Best Pharmaceuticals for Children Act (BPCA), which acts like a "carrot;" it provides an incentive for drug companies to conduct FDA-requested pediatric studies by granting an additional six months of marketing exclusivity
- The Pediatric Research Equity Act (PREA), which serves as the "stick;" it requires pharma companies to study investigational drugs in children under certain circumstances
- The Food and Drug Administration Safety and Innovation Act (FDASIA), which makes *permanent* the BPCA and PREA

So what does FDASIA mean for sponsors?

In 2012, President Obama signed FDASIA into law. FDASIA provides clarity on the process for submitting initial pediatric study plans (PSPs) and amended PSPs, which was first described in the FDA's *Guidance for Industry on Pediatric Study Plans.* FDASIA defines who must submit an initial PSP (iPSP), when it must be submitted, and what it should include. After the end-of-Phase 2 (EOP2) meeting, you have 60 days to submit your iPSP to the FDA. That's an important date. If you don't submit your PSP and are out of compliance, your company may be placed on a non-compliance list on the FDA website. FDASIA also defines what should be included in any requested amendments to an agreed-upon iPSP. Lastly, it specifies a template that should be used to develop an iPSP submission.

The iPSP template

The iPSP template has 12 sections. Here are the sections that contain its major requirements:

Section 1—Overview of the Disease Condition in the Pediatric Population: In this section, the sponsor must provide a brief summary of the pathophysiology of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in the pediatric population including neonates. They also should discuss the incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population.

Section 3—Overview of Planned Extrapolation to Specific Pediatric Populations: In this section, the sponsor must explain their plans for extrapolating efficacy data from adults to pediatrics and provide any available supporting data for all age ranges from which efficacy will be extrapolated. The sources for this supportive data can include sponsor data, published literature, and expert panels and workshops. Extrapolation of efficacy for other drugs in the same class, if previously accepted by the FDA, can also be considered supportive information.

Section 4—Request for Drug-specific Waiver(s): The sponsor must provide their plans and justification for requesting a waiver (either full or partial) of the requirement to provide data from pediatric studies. Requested waivers in the PSP will not be formally granted or denied until the application is approved. If studies are waived because of evidence that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling. Generally, this information is in the Pediatric Use subsection of labels. Waivers to study an investigational drug in pediatric patients are hard to acquire whereas deferrals are easier to obtain.

Section 5—The Summary Plan for Non-clinical and Clinical Studies: In this section, the sponsor lists their planned pediatric clinical and non-clinical studies. The pediatric clinical studies include both pediatric pharmacokinetic studies to determine an appropriate dose based on an established pharmacodynamic endpoint and clinical effectiveness and safety studies.

Section 6—Pediatric Formulation Development: In this section, the sponsor provides details of any pediatric-specific formulation development plans, if appropriate, including whether the formulation that is being developed can be used for all pediatric populations. It also includes information on age-appropriate formulations for all pediatric age groups that will be studied. Sponsors also should provide details about the size of all planned capsules or tablets, to the extent practicable, to be used in pediatric studies.

I'll cite a recent letter to a sponsor developing a pediatric bowel prep drug from the FDA's Division of Gastroenterology and Inborn Errors Products as an example of the evolving attitude towards pediatric drug development. The letter cites the requirement to include an Agreed iPSP. Then, they encourage the sponsor to obtain an Agreed iPSP before submitting a marketing application. The letter ends with a warning that "failure to include an *Agreed iPSP* in a marketing application subject to PREA may be grounds for a *Refuse-to-File (RTF) Action.*"

To me, this suggests that the agency is starting to take a harder line with sponsors who do not abide by PREA requirements. It's more threatening than merely being placed on a non-compliance list on the agency's website. The possibility of receiving an RTF for a product should certainly be an incentive to take pediatric drug development requirements seriously.

The push to leverage pharmacometrics

> *Up to 50% of pediatric safety and effectiveness trials are not interpretable. Unsuitable designs lead to slow enrollment and low retention, as well as higher costs and approval delays.*
>
> —Perdita Taylor-Zapata, MD
> National Institute of Child Health and Human Development

The high failure rate of pediatric clinical trials poses a daunting challenge to the pharmaceutical industry. Pharmacometrics is an important tool to help inform smarter clinical trial designs that maximize insights while minimizing trial duration, number of subjects needed, and number of blood samples taken. The FDA has set a target that 100% of all pediatric trials will have modeling and simulation associated with them by 2020. My company, Paidion, partners with Certara to leverage modeling and simulation for hundreds of studies in early and late pediatric clinical research. We are happy to help you determine how to fit pediatric considerations into your overall drug development program. ■

Best Practices in PBPK Modeling and Simulation

While clinical trials are a mainstay of drug development, there are some questions that you just can't address using this approach. Do I need to adjust my drug's dose in pregnant women? How does drug exposure change in infants? Will my drug's clearance be different in an obese population compared to non-obese patients?

But sometimes, you can get real answers from virtual populations. Certara's physiologically-based pharmacokinetic platform—the Simcyp Simulator—includes extensive demographic, physiologic and genomic databases, which include algorithms that account for patient variability. This enables the user to predict drug behavior in virtual patient populations instead of a virtual reference man, thus allowing individuals at extreme risk to be identified.

This section's blog posts illustrate how PBPK supports a range of drug development applications—supporting formulation development, assessing potential drug-drug interactions (DDIs), and optimizing dosing for special populations. After you read them, you'll understand why we believe that PBPK has evolved from an academic curiosity to a regulatory necessity.

Leveraging PBPK Modeling and Simulation for Neonatal and Infant Drug Development

Alice Ke

Despite increased regulatory support for pediatric drug development, sponsors still face ethical, economic, and practical constraints. Indeed, while children represent about 40% of the world's population, only 10% of the drugs on the market have been approved for pediatrics.

Children are not small adults, and all children are not the same. In particular, children under the age of two are the most heterogeneous. They differ by maturation of organ development, drug metabolizing enzymes and transporters, protein binding, etc.

Neonates—babies from birth to the first month—are the least studied and most fragile pediatric population. In fact, fewer than 5% of pediatric drug trials include neonates. Within the neonatal population, there is a 10-fold difference in weight (0.5–5 kg) between extremely low birth weight preterm infants and full-term infants.

The lack of clinical studies in neonates has resulted in widespread off-label prescribing, leading to under dosing, over dosing, and adverse events. A 2015 analysis in *Clinical Pharmacology and Therapeutics* by Gilbert J. Burckart, PharmD, and his FDA colleagues showed that a total of 44 products had failed pediatric drug development trials submitted to the FDA between 2007 and 2014. Under-dosing was a contributing factor to trial failures in 10 instances. Advances in physiologically-based pharmacokinetic (PBPK) modeling can help inform first-in-pediatric dosing and clinical study design.

The regulatory landscape for pediatric drug development

To address this urgent medical need, both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) now require pediatric trial plans—the Pediatric Study Plan (PSP) and the Pediatric Investigation Plan (PIP), respectively—as part of the approval process for new drugs. In the FDA's 2014 guidance on *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products,* they recommend using modeling and simulation to reduce the uncertainty of dosing pediatric populations. PBPK has been increasingly used in pediatric drug development programs to help optimize pediatric study designs, especially in the 0-2 year old age group.

A brief introduction to PBPK modeling

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.

Overview of the relationships between covariates affecting ADME

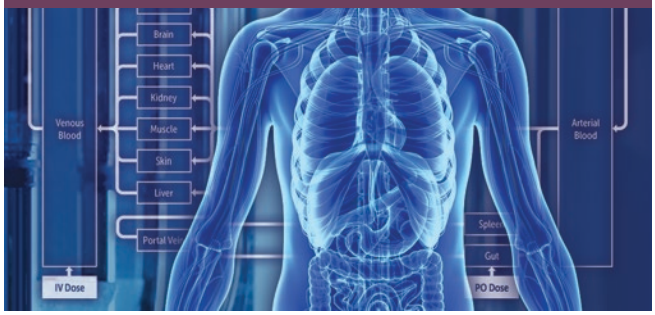
When building virtual human populations for ADME (absorption, distribution, metabolism, and excretion) simulation, the composition of the study group is considered with respect to age, sex, and ethnicity, plus genetic makeup of enzymes and transporter proteins in the target population. However, each factor influences multiple elements of ADME, creating non-linear and non-monotonic relationships. The sensitivity of each pharmacokinetic parameter to a potential covariate depends on the drug and the balance of sensitivities to elements within the network. As drugs differ in their sensitivity to these elements, covariates of pharmacokinetics vary and a "one-size-fits-all" solution cannot be assumed. Prior assessment of covariates ensures that the most relevant factors and the most suitable covariate models are considered during clinical studies.

PBPK modeling applications in pediatric oncology drug development

Childhood cancer represents more than 100 rare and ultra-rare diseases with an estimated 12,400 new cases diagnosed each year in the US. As such, this much smaller patient population presents unique challenges in pediatric oncology drug development. Developing drugs for pediatric malignancies also entails unique trial design considerations including flexible enrollment approaches, age-appropriate formulations, acceptable sampling schedules, and balancing the need for age-stratified dosing regimens given the smaller patient populations. Several published examples in literature showed the successful application of PBPK to projecting the starting doses in various pediatric age groups, to optimizing the sampling scheme, sampling technique (eg, dried blood spots), and calculating sample size. Increasing numbers of PBPK applications are being included in the submission package to support the PIP plan.

Takeaways

PBPK models have the potential to improve pediatric drug development. For children under two years of age, PBPK models can account for developmental changes in liver volume and blood flow, maturation of renal clearance, CYP/UGT ontogeny, and changes in drug absorption in the gut. For children over the age of two, PBPK approaches can help explain complex PK and support bridging formulations from adults to pediatrics. While progress has been made in developing pediatric PBPK models, they are still evolving, particularly for premature babies where some system parameters are "known unknowns." Continued collaboration between academia, industry, and regulatory is critical for establishing best practices in using PBPK to support pediatric drug development. ■



Transforming Drug Product Development the PBPK Way! —A Breakthrough Approach

Shriram Pathak

Developing and optimizing drug formulations—a key component of a product development—is a very lengthy and capital intensive process. Today, most drug candidates are poorly water-soluble; this has led to greater emphasis on screening more complex formulation technologies. Formulation development is still largely an empirical process—based on trial and error and formulation scientists' experience!

Physiologically-based pharmacokinetic (PBPK) modeling has emerged as a valuable resource to support decisions throughout the drug development process. Utilizing PBPK models in discovery programs can support "rational" product development, thereby expediting the process of moving potential active pharmaceutical ingredients (APIs) from discovery to the clinic and subsequent commercialization.

This systematic modeling approach applies to several areas of drug product development such as predicting formulation effects, forecasting food-drug interactions, developing IVIVCs, predicting virtual bioequivalence, justifying biowaivers, and more. In fact, the mechanistic and predictive ability of PBPK models enables exploring the product design spaces more effectively and can facilitate implementing "quality by design" (QbD) in a more meaningful way!

Moreover, the interest of regulatory agencies in the diverse applications of PBPK modeling is reflected in their frequent references in recently approved drug labels, regulatory guidances, and peer-reviewed papers.

The mechanistic, physiologically-based Advanced Dissolution, Absorption and Metabolism (ADAM) Model within the Simcyp Population-based Simulator helps formulation scientists predict the variability in human oral drug absorption from physiochemical and *in vitro* drug data. The ADAM model can simulate a variety of formulations: solutions, suspensions, and immediate release (IR) tablets through to single unit (monoliths) and dispersible dosage forms (viz. gastro-retentive, enteric coated tablets and granules, controlled release (CR) monoliths, and CR dispersions) that release the API over time with or without lag time.

Throughout the years, biopharmaceutical experts from industrial, academic and regulatory organizations have demonstrated how absorption modeling using ADAM can inform formulation development and help generate insights into the product performance *in vivo.* Here we review several such case studies covering different aspects of biopharmaceutics or formulation questions.

Predicting food-drug interactions

Predicting the effect of food on drug exposure, and thereby its safety and efficacy, early in drug development is pivotal to clinical success and to optimal formulation strategy. Current "empirical" methods (such as BCS, BDDCS, and QSAR-based methods) often cannot quantify the magnitude of food effects; this has spurred developing physiologically-based modeling approaches.

With appropriate *in vitro* data, population-based PBPK models can integrate all available physiological (or system) data and drug/formulation-specific information to predict food effects. A range of food-induced physiological changes are incorporated into the ADAM model to simulate the clinically observed phenomena, viz. increased splanchnic blood flow, delayed gastric residence time, dynamic change in the gastric pH, bile salt concentrations, viscosity, and dynamic fluid volumes.

Recently, we successfully predicted the differential food effects on absorption of nifedipine from oral IR and CR formulations using the ADAM model where established rule-based approaches are inapplicable. The study used mechanistic PBPK models with *in vitro* data to predict variations in the PK of the same formulation in the fasted and fed states as well as between different formulations. Anticipating the "formulation specific" food effects in early stages of drug development is of great significance. Applying validated PBPK models, as described in this work, may help formulation scientists in guiding systematic formulation development, reducing undesirable food effects, and avoiding relabeling and safety issues in later stages of product development.

Quantitative prediction of food effect for weakly basic drug compounds is challenging due to their variable dissolution and precipitation in the dynamically changing GI environment. PBPK models can account for these food-induced changes in GI tract and can help predict food-drug interactions. In another such study, researchers leveraged the ADAM model to explore the mechanism(s) behind the differences observed in the duodenal concentration-time profiles and in the magnitude of food effect for two weakly basic, structurally related drugs—ketoconazole and posaconazole.

Food, among a range of other effects, can also alter the viscosity of the GI tract fluids to delay tablet disintegration and potentially reduce drug absorption. In another successful case study, a dynamic viscosity-disintegration model was combined with ADAM and *in vitro* data to anticipate negative food effects upon drug absorption. Dynamic changes to the *in vivo* disintegration rate of an IR formulation of a BCS Class III drug, trospium chloride, was linked to dilutive, time-dependent viscosity changes after food intake.

Using *in vitro* data alone, the ADAM model has also been used to understand the mechanisms underpinning the effect of proton pump inhibitors (PPIs) and acidic carbonated beverages on the oral absorption of drugs. PPIs are OTC products routinely used to treat certain gastrointestinal disorders. PPIs work by reducing the amount of acid in the stomach. As patients are required to administer these medicines for a long period, PPIs may affect the absorption of co-medications. Many people drink soda on a daily basis. Because of their acidic nature, these drinks may alter the gastric environment and thereby may affect the PK of drug compounds. Regulatory agencies require such detrimental changes in drug exposure, if any, need to be tested in lengthy and costly clinical trials. Validated PBPK model can help examine such interactions and may support justifying biowaivers.

These case studies demonstrate that mechanistic model-based approaches integrating both drug and system data have numerous applications, including quantitative food effect predictions, rational formulation design, aiding regulatory approvals by supporting biowaivers, reducing the number of clinical studies, and thus informing better decisions.

Developing mechanistic IVIVCs

The ADAM model can also be used to establish physiologically-based *in vitro-in vivo* correlations (PB-IVIVCs). In cases of significant gut wall and/or hepatic first-pass metabolism of a drug, establishing robust relationships between *in vitro* and deconvoluted *in vivo* dissolution profiles can become difficult, perhaps requiring complex non-linear functions. PBPK-based deconvolution can disentangle these complex processes and estimate *in vivo* dissolution rather than absorption, allowing more robust and simpler IVIVC models compared to the conventional IVIVC methods. Such simplified and usually linear IVIVCs can accelerate formulation development while supporting safety and overall product quality.

This approach has thus far been successfully applied to the development and validation of IVIVC for CR formulations of metoprolol, diltiazem, tramadol, and topiramate. The approach has also been leveraged to CR formulations of BCS II drugs, eg, azithromycin, where absorption is governed by the complex interplay of release, transit/gastro-retention, and permeability rather than just release characteristics.

Recently FDA scientists demonstrated the importance of factoring population variability into metoprolol IVIVC estimation and profile reconvolution. They demonstrated that, in addition to permeation (Peff) and disposition characteristics (Vss/CL) of the individuals using oral solution, gastric emptying time (GET) played a vital role in refining the IVIVC. Factoring out this inter-occasion and inter-subject GET variability during individual deconvolution evidently helped to improve the correlation.

Establishing virtual bioequivalence

Predicting *in vivo* equivalence of drug products virtually is a subject of great interest for pharmaceutical scientists and regulatory agencies. A PBPK modeling approach can predict the population PK variability of a formulated API in a "virtual population" and enable assessing the likelihood of "product bioequivalence" via virtual trials.

Accounting for "variability" in these virtual trials can impact several areas of drug product development, including formulation safe space design, clinically relevant dissolution specification settings, aiding justification of biowaivers, formulation changes in late-stage development, and beyond. Recently, a validated PBPK model of tramadol was used to run virtual bioequivalence (BE) trials; this approach can inform setting dissolution specifications and, consequently, building a safe design space based upon Weibull function parameters.

Additionally, PBPK based virtual trials coupled with pharmacodynamic (PD) models have been used to assess the clinical relevance of bioequivalence criteria. Colleagues at the Brazilian Health Surveillance Agency (ANVISA) constructed a PBPK model for the non-steroidal anti-inflammatory drug (NSAID) ibuprofen and coupled it with two published PD models: antipyresis and dental pain relief. With the help of a validated PBPK-PD modeling approach, the authors demonstrated that the current PK-based BE approach may be too restrictive for ibuprofen products.

Bioequivalence studies are typically conducted in healthy volunteers, but the indicated patient population may have different physiology than a healthy population. PBPK models hold an advantage over other modeling approaches as they account for both the drug formulation characteristics and the underlying physiology of the species studied and its co-variates within a population. Hence, PBPK models can "extrapolate" to other populations, such as pediatric or bariatric surgery patients, where conducting clinical studies is quite challenging! In this context, scientists demonstrated how PBPK-based virtual trials can assess product performance of two weakly basic drug compounds—ketoconazole and posaconazole—in a variety of patient populations and clinical situations.

A novel biopharmaceutical-IVIVE paradigm

In vitro-in vivo extrapolation (IVIVE) techniques translate parameters derived from *in vitro* experiments to their corresponding *in vivo* counterparts to predict the *in vivo* behavior of drug candidates. The Simcyp *In Vitro* Analysis (SIVA) toolkit is a user-friendly software package designed to help pharmaceutical scientists analyze complex data generated from dissolution techniques such as USP II, USP IV, transfer model, two-phase dissolution model, etc. This approach may also help formulation scientists to estimate unknown/uncertain parameters of the drug product, ie, particle size, drug precipitation parameters, etc., that are generally unavailable in early product development. Moreover, this approach streamlines and optimizes designing *in vitro* experiments to potentially reduce the cost and time of formulation development.

Various examples of biopharmaceutical IVIVE, viz. danazol (modeling USP II dissolution), dipyridamole (conventional USP II vs. two-phase dissolution modeling), ketoconazole (transfer experiment modeling), and posaconazole (changing dissolution media modeling), demonstrate that PBPK modeling informed by mechanistic modeling of *in vitro* experiments increases confidence in the quality of the input parameters and mechanistic models used for *in vivo* simulations.

Over the years, PBPK modeling has transformed from merely an early-stage modeling tool to a mature field with proven potential to reduce and refine clinical trials to study drug-drug interactions and drug effects in special populations. However, its applications in biopharmaceutics and formulation studies have not been explored extensively. Recent advances and applications in the use of Simcyp represent an opportunity for formulation/experimental scientists to explore modeling in designing and/or screening formulations. Using validated predictive modeling techniques will lead to more rational drug development. ■

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Using PBPK Models to Optimize Anti-HIV Drug Dosing in Pregnant Women

Angela Colbers

Antiretroviral drugs are a critical tool in preventing mother-to-child transmission of HIV. Yet, antiviral treatment options for pregnant women lag behind the "non-pregnant" population. In this blog post, I'll discuss the reasons for this lag and how physiologically-based pharmacokinetic (PBPK) models can simulate PK during pregnancy and thus help optimize dosing for this special population.

Preventing mother-to-child HIV transmission

In 2016, approximately 1.4 million HIV-infected women in the world gave birth. Without the intervention of antiretrovirals, the risk of HIV transmission from mother to child is 15–40%. With antiviral treatment, the transmission risk is reduced to less than 1%. Thus, we can reduce the possible new infections from 560,000 to less than 14,000—a great achievement.

Unfortunately, the treatment options for pregnant HIV+ women lag behind the treatment options for non-pregnant women or men. For example, dolutegravir, elvitegravir, and TAF—routine treatments for non-pregnant HIV+ patients—are either not available or are not preferred treatment options for pregnant women.

Why do treatment options lag behind for pregnant women?

Pregnant women are usually excluded from clinical trials of investigational drugs because the risk posed to the unborn child is unknown. We do gain some insight into how these drugs perform during pregnancy after they are approved as the pharmaceutical companies maintain pharmacovigilance registries of pregnancy cases and outcomes. Also after drug approval, academic groups may perform pharmacokinetic studies in pregnant women.

Thus, there is a delay between FDA approval of a drug and data on its impact on pregnancy becoming available. For most of the older antiretroviral drugs, pregnancy information became available within two years after FDA approval. But the lag is much longer for newer treatments—six to eight years. And we have no data for the newest marketed compounds—dolutegravir, elvitegravir, cobicistat, and TAF.

Understanding how drugs perform in pregnancy is crucial to optimizing maternal care. Despite antiretroviral therapy, approximately 13% of pregnant women still have a detectable viral load at the time of delivery. Adequate maternal exposure to antiretroviral drugs is necessary for maximal reduction of viral loads and reduced risk of transmission.

Physiological changes during pregnancy can influence PK

An array of physiological changes that occur during pregnancy can affect the absorption, distribution, metabolism, and excretion (ADME) of drugs. Regarding drug absorption, gastric pH, gastric emptying, and intestinal motility change during pregnancy. As a pregnant woman gains weight, her volume of distribution increases as well. For metabolism, hepatic blood flow, some CYP enzymes' activity, and renal excretion also increase.

The overall effect of pregnancy on drug exposure depends on the drug being administered. For darunavir, its concentrations during pregnancy are decreased. By contrast, etravirine concentrations are higher during pregnancy. The mechanism behind these changes is likely because CYP2C19, which metabolizes etravirine, is inhibited during pregnancy whereas CYP3A4, the main enzyme metabolizing darunavir, is induced.

Characterizing antiretroviral drug PK in pregnant women

To investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women, my colleagues and I established PANNA, a European clinical pharmacology network. It's a general study protocol for investigating over 18 antiretroviral drugs. Pregnant HIV+ women who are using at least one of these drugs can participate in the study.

The PANNA study protocol involves the following steps: We collect a full pharmacokinetic curve during the third trimester of pregnancy and again 4–6 weeks postpartum. We derive pharmacokinetic parameters from these curves using Phoenix WinNonlin and make an intrasubject comparison with the postpartum curve as the control curve. At delivery, we also try to obtain a cord blood sample to assess whether these drugs cross the placenta. The PANNA study is currently running in 25 hospitals in seven European countries. Unfortunately, it's fairly burdensome for the patients to spend an entire day at the hospital to develop a PK curve.

To make it easier to study these pharmacokinetic changes, we next developed the "PIANO" project: Pharmacokinetic Investigations of Antiretroviral agents in HIV-infected pregNant wOmen. The aims of the PIANO study are:

- To develop a PBPK model that simulates maternal pharmacokinetics in pregnancy
- To support better dose predictions for this patient population and anticipate the effects of drug interactions and co-morbidities on exposure
- To identify knowledge gaps that limit the accuracy of PBPK modeling

The PIANO approach

To develop the PBPK model, we used the Simcyp Simulator 13.2 pregnancy model. *In vitro* ADME parameters for input into the PBPK models were determined experimentally or were based on literature. Model predictions were validated with the results from the PANNA study.

We chose to model darunavir (DRV) PK as it is a preferred antiretroviral for use in pregnancy. DRV is a CYP3A4 substrate, and the antiretroviral ritonavir (RTV) inhibits CYP3A4. Thus, co-administration of DRV and RTV increases the DRV concentration. For this reason, DRV is always

combined with RTV as a booster. So, we had to model the interaction of these two drugs in addition to the effect of pregnancy.

Building the model

The first step was to develop a PBPK model for a single dose of un-boosted DRV. Clinical data were available to validate this model. Then, we included RTV as a booster to the model and simulated the interaction between a single dose of DRV + RTV. Next, we simulated the steady state exposure of DRV + RTV in a non-pregnant population before performing this simulation in the pregnant population. Lastly, we simulated some dose adaptations in a virtual pregnant population.

When we simulated a single dose of darunavir with our first model, we over-estimated the exposure. What could be the reason for this? This model didn't include transporters. Both uptake and efflux transporters play a role in darunavir pharmacokinetics. But, we didn't have quantitative data available that described these darunavir transporters like KM, V_{max}, or intrinsic clearance. When we included transporters in the model, its predictions were much closer to observed data.

The next step was to include ritonavir in the model. Then we performed simulations for both dosing regimens for darunavir: 600/100mg DRV/RTV BID and 800/100mg DRV/RTV QD and calculated DRV's C_{max} and AUC for both regimens. This model had reasonably accurate predictions; DRV PK parameters were within a twofold difference from observed data.

Finally, we modeled DRV + RTV PK in pregnant patients in their third trimester as well as postpartum. We again simulated both dosing regimens. For the twice daily dosing regimen, the model showed that DRV exposure was lower in the third trimester of pregnancy than postpartum. The model's predictions were robust for both the third trimester and postpartum. The same was true for the once daily DRV+RTV regimen. The model's fit was not as good but was still within a twofold difference from observed data. Again, the model predicted lower DRV exposure during late pregnancy compared to postpartum.

Take home points

As with all models, our model has some uncertainties and limitations. The role of hepatic uptake, efflux transporter intrinsic clearance, and intestinal transporters in DRV PK have yet to be determined. The ritonavir model was a semi-mechanistic model. For darunavir, its absorption was not fully mechanistic, but rather employed a top-down approach. Importantly, while our model assessed maternal exposure, it could not assess fetal exposure.

To summarize, our data supported a clinically relevant role for hepatic transporters in darunavir pharmacokinetics. In addition, the described model could approximate boosting by ritonavir and the decrease in maternal darunavir exposure observed during pregnancy.

To improve the mechanistic basis of the model, future studies should address hepatic and intestinal transporter-mediated darunavir disposition in greater detail. This development of the model has been published in *Clinical Pharmacokinetics.* The PBPK modeling approach has the potential to provide a greater understanding of the mechanisms of drug disposition in pregnancy and help optimize dosing for pregnant women. ■

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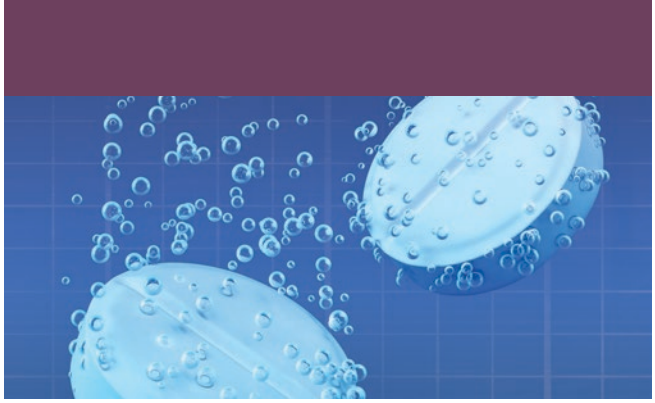

PBPK Modeling of Supersaturating Drug Product Behavior

David Turner

The problem of supersaturating drug products might loosely be summed up as: *"If you're not part of the solution, you're part of the precipitate!"*

Indeed, more than 60% of new drug candidates are poorly soluble[1] which can severely limit their bioavailability. To ameliorate this issue, a common approach is formulating to create supersaturated solutions of a drug. Widely used approaches include, for example, using amorphous solid dispersions, where the amorphous solid has higher solubility than a more stable crystalline form or formulating the drug as a salt. In both cases, the dissolution of the formulation results in concentrations of dissolved drug that exceed the thermodynamic solubility. Such supersaturated solutions therefore carry a precipitation risk which can severely limit the intended benefits of this approach but which can be ameliorated through additional formulation strategies such as the addition of precipitation inhibitors. In addition, poorly soluble, low basic pKa drugs, which tend to have significantly higher solubility at the low gastric pH typical of fasted conditions compared to the elevated pH of the small intestine, are also susceptible to precipitation. Thus, anticipating these properties and reacting accordingly, for example through adding precipitation inhibitors, can be critical to successful drug development.

The Office of Generic Drugs (OGD) at the US Food and Drug Administration (FDA) recently awarded Certara's Simcyp group a multi-year research grant to create and validate a physiologically-based pharmacokinetic (PBPK) modeling and simulation framework to predict and simulate the behavior of supersaturating, orally dosed drug products in the human gastro-intestinal tract. This platform will also permit assessing and comparing new products to reference products.

We aim to further develop state-of-the art mechanistic models and workflows to improve predicting the *in vivo* behavior of supersaturating drugs. The models should help sponsors to employ appropriate formulation strategies and either prevent precipitation or mitigate its impact earlier than before.

The Simcyp Population-based Simulator is designed to simulate clinical trials and predict variability between individuals in different populations rather than just for an "average person". The Simulator already includes a sophisticated and well recognized oral absorption module—the Advanced Dissolution Absorption and Metabolism (ADAM) model.[2-7] The Simulator is complemented by the separate Simcyp *In Vitro* Data Analysis (SIVA) Toolkit.[5] This tool is essential for gaining/confirming mechanistic understanding, model validation, and in certain situations, for extracting appropriate parameters from *in vitro* experiments for use as input for *in vivo* simulations.

Predicting supersaturation and precipitation kinetics of drugs and drug products in the complex, variable GI luminal environment is a challenging task requiring both suitable mechanistic models and detailed descriptions of physiology and its patient to patient variability. Precipitation from supersaturated solutions is usually characterized by two processes, viz. a nucleation step and a precipitation step. Many mechanistic models are available for handling nucleation; the most well-known is Classical Nucleation Theory (CNT). We will also investigate alternatives as part of this project, including tools to deal with liquid-liquid phase separation phenomenon, which cannot be dealt with using CNT. The relevant physiological parameters for modeling events in the GI tract include: luminal fluid volumes and their dynamic changes when a glass of water is taken with a dosage form; pH and bile salt concentrations; transit rates including gastric emptying; luminal fluid viscosity and flow rate; buffer capacity; gut wall permeability (both passive and active), and a number of other factors, *all* with inter-individual variability.

The mechanistic supersaturation and precipitation models and the supporting physiology and variability database will be validated against clinical studies performed under the auspices of Professor Augustijns of the Drug Delivery and Disposition Unit in the Department of Pharmaceutical and Pharmacological Sciences at the University of Leuven. Some of the clinical studies available with supersaturating formulations include simultaneous measurements of drug concentration in luminal fluids[4] and in the plasma providing dual endpoints against which to assess the PBPK models.

Given the complexity of the nucleation process and crystal growth, this project is not expected to solve all the associated issues. However, the undertaking will be a significant advance both in terms of identifying appropriate and sufficient mechanistic models and the provision of tools to enable the transfer of information from appropriate *in vitro* experiments to simulations of *in vivo* behavior within a PBPK modeling framework. ■

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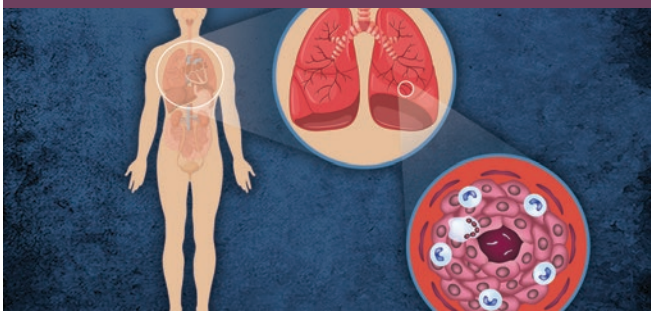

New Tools Support Developing Better TB Drugs

Iain Gardner and Oliver Hatley

Tuberculosis (TB)—caused by *Mycobacterium tuberculosis* infection—is one of the top 10 leading causes of death worldwide with a total of 1.8 million people dying from the disease in 2015. TB is also the leading cause of death in HIV-infected individuals. TB usually attacks the lungs but can infect any part of the body. A hallmark of pulmonary TB is the formation of mycobacteria-containing granulomas—heterogeneous lesions composed of a macrophage- and neutrophil-rich cellular rim surrounding a necrotic core. To effectively treat TB infections, drugs have to move from the site of administration (usually the intestine following oral administration) into the blood stream and from there they need to effectively distribute into the lung tissue and attain sufficient concentrations within the granuloma to kill the mycobacteria. The lack of correlation between the administered dose and the drug concentration in the plasma, lung, and granulomas is thought to contribute to the need for long treatment durations and also to the failure of novel drug regimens.

Most TB drugs are more than 40 years old, have significant side effects and drug interactions, and require long treatment periods (treatment courses usually last for at least 6 months). In addition, strains of *M. tuberculosis* resistant to the standard of care drugs have begun to emerge. These challenges with current anti-TB therapy have led to attempts to improve TB treatment regimens and to develop novel anti-TB drugs. In this blog post, I'll discuss our work with the Critical Path to TB Drug Regimens (CPTR) Initiative to develop new modeling and simulation tools to help drug developers combat TB.

The CPTR Initiative is a cross-sector initiative to develop novel approaches to expedite new, safe, and effective TB treatment regimens with shorter therapy durations. As part of this mission, the Regulatory Science Consortium for the CPTR Initiative, led by the Critical Path Institute, coordinates collaborations to develop quantitative platforms to revamp drug development.[1]

Building a more physiologically-relevant lung model

In an effort to allow drug developers to gain a better understanding of new and existing anti-TB drugs in the lung and granuloma lesions, CPTR and C-Path partnered with colleagues in the Certara Strategic Consulting and Simcyp groups to develop a multiple-compartment, permeability-limited model of the human lung.[2] The final model structure (representing the lung and airways as 7 compartments) balances a realistic representation of lung physiology with reasonable computational speed. Built to work in conjunction with our Simcyp Population-based Simulator, this model can predict the disposition of drugs within the plasma, lung, and epithelial lining fluid (ELF) and the potential impact of disease progression on drug kinetics at different stages of TB infection. The model also allows regional physiological differences in gas exchange, blood perfusion,[3,4] and transporter expression in the lung[5] to be considered as these differences may affect local drug concentrations and efficacy.

Extending the multiple-compartment, permeability limited lung model

The first iteration of the multiple-compartment, permeability-limited lung model assumed only passive movement of drugs within the lung compartments.[2] However, some drugs such as moxifloxacin, an antibiotic being tested in anti-TB regimens, are transported by drug transporters such as P-glycoprotein (P-gp).[6]

To account for the action of P-gp in the lung, a full body physiologically-based pharmacokinetic (PBPK) model was constructed for moxifloxacin in the Simcyp Simulator[7] with disposition in the lung being represented by the multiple-compartment, permeability-limited model.[2] The *in vitro* intrinsic clearance of moxifloxacin by P-gp was estimated using the Simcyp *In Vitro* Analysis (SIVA) toolkit and was extrapolated to the *in vivo* situation by accounting for differences in surface area and assumed differences in transporter expression between the *in vitro* system and the lung *in vivo*.[6] Including P-gp transport in the PBPK model of moxifloxacin improved the accuracy of the prediction of ELF:plasma ratio for this drug.

Finally, the multiple-compartment, permeability-limited lung model was extended to describe drug disposition within a tuberculosis granuloma. The mechanistic, multi-compartment granuloma model includes compartments representing macrophages, interstitial fluid, caseum, and blood.[8] Four drugs, with different dosing regimens, can be studied concurrently with this model. This is especially important as the most common dosing regimen for TB uses four drugs.

A new tool in the war against TB

This newly developed PBPK model can help drug developers leverage *in vitro* and *in silico* data to better understand drug disposition and penetration in plasma, lung tissue, ELF, and TB granulomas. In addition, these tools will allow researchers to simulate a range of variables—drug dose, disease state, and concomitant medications—and thus support designing more effective drug regimens. Likewise, these modeling and simulation tools could potentially support personalized dosing for TB patients. Using model-informed drug development approaches is a critical weapon in winning the war against the global TB scourge. ■

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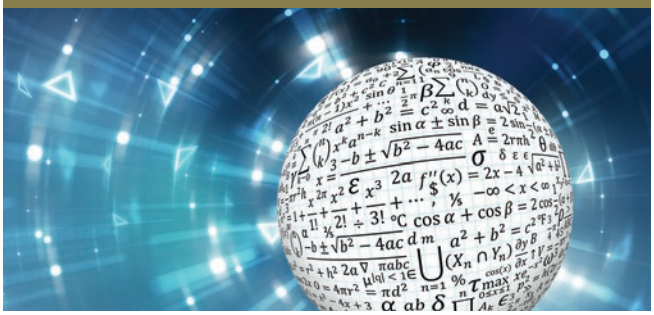
PK/PD Modeling and Simulation Trends to Watch

Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials.

—US FDA Commissioner Scott Gottlieb, MD

Phoenix is the most advanced, intuitive, and widely-used software for pharmacokinetic (PK), pharmacodynamic (PD), and toxicokinetic (TK) modeling and simulation (M&S). It is used by 6,000 researchers at 1,500 biopharmaceutical companies and academic institutions in 60 countries. Phoenix is also employed by many global regulatory agencies for submittal review, including 11 divisions of the US Food and Drug Administration (FDA).

At Certara, we take our responsibility to deliver continuous improvement and innovation very seriously. Please enjoy these blog posts on some of the latest innovations in and applications of PK/PD M&S.



Modeling Delayed Outcomes in PK/PD Studies Using DDEs

Shuhua Hu

Delays are ubiquitous in pharmacokinetics (PK) and pharmacodynamics (PD) studies. Transit compartment models, described by systems of ordinary differential equations, have been widely used to describe delayed outcomes in PK and PD studies. The obvious disadvantage for this type of model is it requires manually finding proper values for the number of compartments. In addition, it may require many differential equations to fit the data and may not adequately describe some complex features.

Delay differential equations (DDEs) provide an alternative way to model delayed outcomes that does not suffer these disadvantages. In this blog post, I will introduce DDEs and demonstrate their relationship with traditional models such as transit compartment models, typical absorption models, and models for describing atypical absorption profiles.

Why is modeling delays important?

Delays commonly occur in pharmacology. For example, have you ever had a headache and noticed that there is a delay between the time you swallow some ibuprofen tablets and the time when you start feeling better? This is due partly to an absorption delay arising from the time it takes for the drug to be transported from the depot site to the central compartment after drug administration. Some drugs are administered as pro-drugs that must be metabolized to the active drug. In these cases, the drug effect may be delayed with respect to the parent drug concentration in the central compartment.

Introducing DDEs

For ordinary differential equations, the future state of the system is totally determined by its present value. While for delay differential equations, the future state of the system is determined by both its present *and* past values. This means that for DDEs, one has to specify the history function, which gives the behavior of the system prior to time 0 (assuming that we start at t = 0).

Delay differential equations have been widely used in the biological sciences and engineering to model delayed outcomes. The first biological application of DDEs for investigating predator-prey interaction dynamics dates to the 1920s. However, this approach did not become widely adopted until the 1970s. In recent years, we have seen DDEs starting to be used for pharmacological applications.

The discrete delay approach

Differential equations that only involve discrete delays are called discrete delay differential equations. Viral dynamics have been modeled using discrete DDEs. For example, the human immunodeficiency virus infects CD4+ T cells. A temporal delay exists between the time of the initial T-cell infection and the onset of viral production. The HIV kinetics model that uses discrete DDEs assumes that the length of time from the initial infection to viral production is the same for all acutely infected T-cells. But, this is not true in reality. How do we accommodate the fact that the delay time varies between infected cells?

The distributed delay approach

If you use a weighted average for all possible values for the delay time, you get the convolution of the signal to be delayed and the probability density function (PDF) of the delay time. This type of delay is referred to as a "distributed delay." The PDF of the delay time is often called the "delay kernel."

The distributed delay approach includes the discrete delay approach as a special case. It also incorporates a wide array of pharmacokinetics and pharmacodynamics models as special cases including transit compartment models, typical absorption models, and a number of atypical (or irregular) absorption models. This is done through assuming a specific distribution form for the delay time.

Bringing the power of DDEs to pharmacometrics

Phoenix NLME offers integration of a model delay (discrete or distributed) function, eliminating the need to add complex lines of code for each delay differential equation. The new delay function greatly simplifies modeling delayed outcomes, an important function in several therapeutic areas such as oncology, diabetes, and arthritis. In Phoenix 7.0 you can add a delay function with a single Phoenix Modeling Language (PML) command, avoiding inefficient workarounds and approximations. I look forward to seeing how this new approach will help sponsors gain a better understanding of physiological and pharmacological systems that invoke temporal delays. ■

Using Pharmacokinetics to Assure Chemical Food Safety

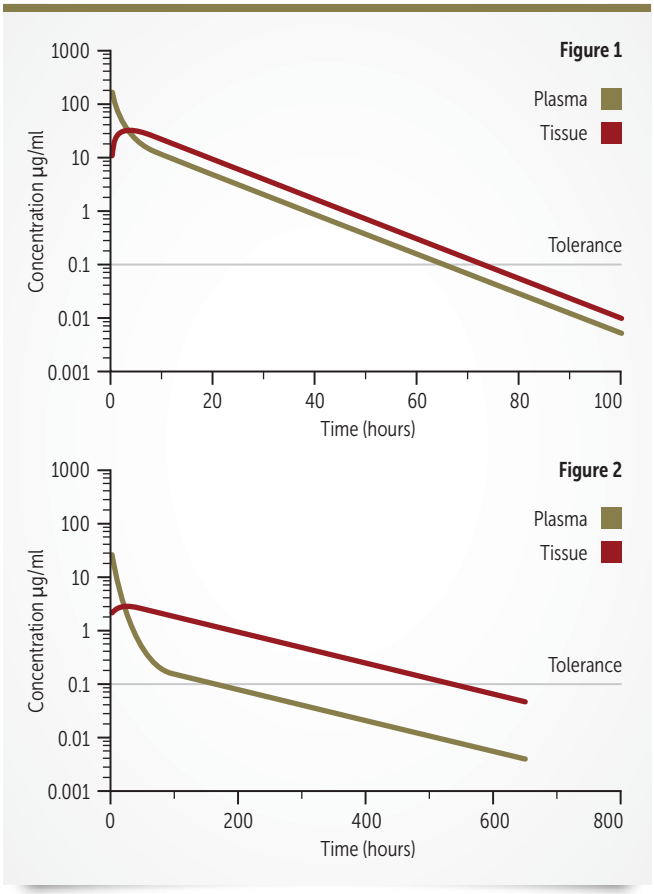
Ronette Gehring

As a veterinarian, I'm responsible for the health and welfare of my animal patients. Sometimes, drugs are used to treat animals that are being raised for food (eg, meat and milk). Therefore, tissue residues are a unique concern in veterinary medicine because indirect exposure to drugs and their metabolites through eating meat or milk could potentially negatively impact human health. For this reason, we need to be able to make robust predictions of the time delay for tissue drug residues to fall below concentrations that have been shown to be safe for human consumption (the "tolerance"). The plasma elimination half-life is the pharmacokinetic (PK) parameter that reflects a drug's persistence in the body. A challenge for predicting tissue residues is that they may persist beyond when plasma concentrations can be detected with even the most sensitive bioanalytical method.

Compartmental PK models can be used to describe plasma time-concentration data. These models capture the different rates at which a drug distributes to and from the various tissues of the body. These rates are dependent on how the physico-chemical properties of the drug interact with the characteristics of each tissue. In compartmental PK models, a compartment represents a group of tissues to which the drug distributes and equilibrates at the same rate. The number of compartments in the model determines the number of exponential terms needed to describe the plasma time-concentration curve.

As analytical techniques become more sensitive, ever lower plasma drug concentrations can be measured, and more compartments may be needed to fully describe a drug's plasma time-concentration profile. If the analytical method is sensitive enough, it becomes possible for the terminal elimination phase to represent the half-life and persistence of the drug in the tissue from which it depletes the slowest (deep compartment), making it relevant to human food safety. Examples of groups of drugs for which the number of compartments increased with increasing sensitivity of the bioanalytical technique include the antibacterial tetracyclines and aminoglycosides.[1,2]

Using a published model for oxytetracycline,[1] the consequences of using a two- versus a three-compartment pharmacokinetic model to predict tissue drug concentrations is illustrated in Figures 1 and 2, respectively. Notice that the two-compartment model greatly under-predicts the tissue concentrations and the time needed for them to deplete to levels that are below the tolerance. For this reason, regulatory withdrawal times (official withdrawal times that appear on the label of a pharmaceutical product approved for food-producing animals) must be based on tissue data collected from animals that are sacrificed at sequential times after treatment. Models based on plasma data can be used to estimate an appropriate waiting time before animals can be slaughtered following the extra label use of a drug, and they have the advantage that animals do not need to be sacrificed. But this is only possible if the analytical method is sensitive enough to pick up the concentrations associated with the deepest compartment that represents the tissue from which the drug depletes the slowest.



I hope that you know have a better understanding of how pharmacokinetic modeling can be used to predict drug persistence in milk and meat and thus help ensure food safety.

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Feedback from the Phoenix Community: Our Visits with the FDA

Nathan Teuscher

We recently completed a week-long set of meetings with the FDA, where we met with over 300 FDA reviewers from 7 of the 11 FDA centers that use Phoenix.

Here are a few topics that took center-stage during our visits:

Q: How can we create Phoenix workflow templates that are reusable across different studies with varying numbers of parameters, such as treatments, analytes, matrices, and doses?

A: Creating workflow templates in Phoenix—containing a single object (like an XY plot) or multiple objects (eg, an entire workflow or set of objects)—is an effective way to increase your productivity. An example of a workflow template that is of particular interest for generic drug development is one that can be used for reference-scaled average bioequivalence (RSABE) methodology, which is increasingly used to demonstrate bioequivalence for Highly Variable Drugs and Drug Products (HVDs/HVDPs). For more information on workflow templates, be sure to check out our blog posts on how to create a Phoenix workflow template and how to use the Phoenix RSABE templates. If a more complex automated template is required, learn about implementing custom solutions using our Phoenix Technology Services.

Q: What is the advantage of using the QRPEM engine for population pharmacokinetic/pharmacodynamic (PopPK/PD) analysis that was introduced in the latest version of NLME 7.0?

A: The Quasi-random Parametric Expectation Maximization (QRPEM) algorithm is the most advanced and fastest accurate likelihood expectation maximization (EM) algorithm available, ideal for converging complex models such as those used in PopPK/PD modeling. QRPEM addresses problems typically encountered in the PopPK/PD NLME domain, resulting in the ability to achieve N-1 behavior, and greatly improves computational efficiency for models where fixed effects cannot be driven by a simple EM update based on the estimated mean and covariance matrix of the posterior distributions for each subject. Download our white paper for a comprehensive overview of the NLME QRPEM algorithm.

Q: How easy is it to set up a grid?

A: The performance and scalability of software and hardware always constrains a PK/PD modeler's productivity. The explosion of cloud computing resources has provided access to significant computing power to solve these complex models. However, accessing these cloud computing systems can be complex and confusing. And using these systems generally requires knowledge of command-line tools. To improve the performance of computationally intensive algorithms, parallel computing functionality was introduced in Phoenix NLME 7.0. This innovation enables modelers to easily access the power of these computing environments from the comfort of their desktop.

We welcomed the opportunity to get important feedback from the FDA to help us make Phoenix an even better product for our users! ■

The Next Big Thing in Modeling and Simulation: Quantitative Systems Pharmacology and Quantitative Systems Toxicology

Quantitative systems pharmacology (QSP) and quantitative systems toxicology (QST) are relatively new disciplines with enormous potential to improve pharma R&D productivity. Most major pharma organizations are investing in these systems-based approaches to pharmacology and toxicology. Both QSP and QST may also be able to take advantage of the enormous amounts of information we now have access to, including genomics and proteomic data.

QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. This emerging discipline integrates quantitative drug data with knowledge of its mechanism of action. QSP models predict how drugs modify cellular networks in space and time and how they impact and are impacted by human pathophysiology. Additionally, QSP facilitates evaluating complex, heterogeneous diseases such as cancer, immunological, metabolic, and CNS diseases that probably will require combination therapies to fully control them.

QST is a multidisciplinary approach, which, at the juncture of systems biology with toxicology and chemistry, integrates classical toxicology with quantitative analysis of the molecular and functional changes that occur across multiple levels of biological organization. QST aims to characterize adverse drug reactions (ADRs) by describing modes of action as adverse outcomes pathways and perturbed networks versus conventional empirical end points and animal-based testing.

In 2017, we invested big in QSP and QST. And we predict that their role in informing drug development is only going to grow. Read the blog posts in this section to learn how we're leading the way in systems biology approaches.

Mechanistic Modeling of Genome Scale Molecular Interaction Networks

Andrzej Kierzek

Upon the completion of the Human Genome Project, the lead investigator, Dr. Francis Collins remarked:

> *Science is a voyage of exploration into the unknown. We are here today to celebrate a milestone along a truly unprecedented voyage, this one into ourselves. Alexander Pope wrote, "Know then thyself. Presume not God to scan. The proper study of mankind is man." What more powerful form of study of mankind could there be than to read our own instruction book?*

The critical technique used in the Human Genome project—DNA sequencing—is a disruptive technology. The ability to sequence an individual person's genome is likely to substantially impact how we use medications to treat patients.

Untangling the genotype-phenotype relationship

How does the behavior of cells, tissues, organs, and organisms emerge from interactions between the genome and environment? Currently, this question is mostly addressed by looking for statistical associations between the full genome sequence and phenotypic traits. Genome-wide association studies (GWAS) can lead to discovering genetic loci associated with different phenotypes, including increased disease susceptibility. While impressive and certainly valuable, GWAS does not answer *how* a patient's genetic polymorphisms contribute to increased disease susceptibility. Without knowing the underlying mechanisms of these associations, it's difficult to use this information to design therapeutic interventions. Also, we are frequently interested in explaining genome-environment-phenotype interactions involving factors such as exposure to drugs and/or toxins, diet, or exercise. But, studying these more complex interactions using an approach based solely on statistical association is challenging.

Mechanistic simulation of the genotype-phenotype relationship

Mechanistic modeling is an alternative to statistical approaches that can yield greater understanding and predictive power. I've spent most of my academic career performing mechanistic modeling of the genotype-phenotype relationship.

Fortunately, we know *a lot* about the molecular biology of the cell. PubMed contains millions of articles describing individual interactions between molecular components of the cell. How can we represent this knowledge as a computer model capable of simulating the dynamics of a cell's molecular components? The molecular machinery of the cell knows how to express the genome in the context of a particular environment. If we could reverse engineer this machinery in the form of a computer model, we could use it to predict the phenotype arising from the interaction of the environment and a genotype. For a given genetic polymorphism, the model would simulate the dynamic response to environmental conditions.

The rise of PBPK

Modeling the entire molecular biology of cells is a daunting task. So how can we create large-scale mechanistic models with predictive power sufficient for drug developers? The acceptance of physiologically-based pharmacokinetic (PBPK) modeling by industry, academia, and regulators gives me reason to be optimistic.

PBPK is a mechanistic approach for describing the dynamics of drug absorption, distribution, metabolism, and elimination in physiological compartments. The variables of the model are the drug concentrations in physiological compartments. The dynamics of these variables are modeled by the system of ordinary differential equations using compartment volumes, blood flows, and partition coefficients as parameters. These parameters are based on the human physiology literature and *in vitro* assays rather than estimated for each study. The model is then used to simulate the dynamics of the drug's concentration at the site of action.

The whole-body PBPK models used today contain "models within models." The physiological compartments are subdivided into smaller compartments and new, intra-organ flows are defined. Certara's Simcyp Simulator contains mechanistic models of the gut, lung, kidney, brain, and liver. The general method of building this large-scale model is the same as building models of intracellular networks: literature knowledge and *in vitro* assay data are represented by a computational model.

Use of large-scale, mechanistic models by industry regulators

Performing simulations using PBPK models lets us use this knowledge to predict the behavior of the system. In fact, predictions based on PBPK simulations have been accepted by regulators as the sole evidence for assessing certain types of drug-drug interactions (DDIs). Thus, we can bypass performing clinical trials to quantify these DDIs.

And this example isn't an isolated case. Around 100 label claims have now been informed by PBPK simulations. To me, this suggests that it's possible to build large-scale, literature-based mechanistic models with predictive power sufficient for the most stringent application: regulatory submission.

Extending mechanistic modeling to account for all human genes

The whole-body PBPK model of the Simcyp Simulator accounts for about 20 genes encoding drug metabolism enzymes and transporters. Genetic polymorphisms in the population of interest can be input into the software and used to simulate the PK variability expected in a particular trial. However, there is huge gap between this mechanistic model and incorporating the full genetic code of the patient—around 30,000 genes. How can we extend mechanistic models to account for all genes and interpret -omics data (genomics, metabolomics, proteomics, etc.) by mechanistic simulation rather than statistical association?

One answer involves building mechanistic models of molecular networks operating in intracellular space. Genome scale metabolic networks (GSMNs) are models that account for thousands of genes. Integrating PBPK with GSMN and gene regulation models can extend the scope of mechanistic pharmacokinetic modeling to provide greater insights into drug mechanisms. ■

Quantitative Systems Toxicology—Taking the Cue from Aristotle

Maria Saluta

The whole is greater than the sum of its parts.

—Aristotle

This quote from the great 4th century BCE Greek philosopher and scientist has become the mantra for many endeavors, sectors, organizations, and disciplines. From biology, chemistry, and physics to agriculture, engineering, and business, it is the foundation for synergy.

What is the connection between Aristotle's famous quote and quantitative systems toxicology (QST)? QST's origins lie in systems biology, which asserts that biological systems have properties that emerge from a system as a whole rather than its constituent parts. Systems biology applies a non-linear, integrative, quantitative, and holistic approach using an interdisciplinary mix of biology, computational modeling, engineering, bioinformatics, and other sciences to understand complex biological systems. The underlying basis of "the whole is greater..." in systems biology is to decipher how complex interactions give rise to the function and behavior of biological systems, eg, cell signaling networks. In other words, systems biology can be looked upon as a "network of networks:" how all components inter- and intra-connect and change in response to perturbation. The foundation for this approach lies with the emergence and evolution of "omics" technologies—genomics, proteomics, metabolomics, transcriptomics, and others.

QST sits at the juncture of systems biology with toxicology and chemistry. It integrates classical toxicology with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organization. Sponsors employ QST to characterize adverse drug reactions (ADRs) and predict toxicity early in the drug discovery process. Current pre-clinical animal tests and modeling technologies fail to predict around 30% of ADRs. These knowledge gaps impede the development of new, efficacious drugs. The availability of omics data and advanced computational and high

throughput screening tools has spurred the move towards using QST models to better understand ADR mechanisms to achieve more predictive and accurate risk assessment.

QST integrates *in vitro* and *in vivo* toxicity data with a large computational network approach to risk assessment. Keeping with Aristotle's "whole is the sum of its parts" theory, the "sum" of QST "parts", eg, reliable models, pathway knowledge, high content technologies, linking perturbations to adverse outcomes, addressing uncertainty, and developing pathway-based test strategies, will result in the "whole"—effective and safer drugs.

Aristotle also stated, "All men by nature desire knowledge." This quote also applies to QST by providing insights into the link between molecular interactions and adverse effects. There is also substantial potential that QST offers to drug discovery and development: lowering the cost and time to bring new drugs to market, better predictive models for adverse effects, increasing drug efficacy, reducing ADR risk, and reducing animal testing are only a few of the benefits that can be derived from QST. I believe Aristotle would be quite pleased, as a scientist and scholar, with how his philosophies have contributed to the field of quantitative systems modeling.

At Certara, we're exploring a systems approach to pharmacology and toxicology. Quantitative systems pharmacology (QSP), another subset of systems biology, combines computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process. Earlier this year, we launched the Systems Pharmacology Immunogenicity Consortium fashioned after our Simcyp Consortium. We have also begun looking at how we can lend knowledge and tools to advance the quantitative systems toxicology approach. In the tradition of Aristotle, these initiatives will help us understand how toxicological phenomena emerge from complex interactions between drugs and human physiology. ■

Using Model Reduction to Bridge the QSP-Pharmacometrics Divide

Tom Snowden

Quantitative systems pharmacology (QSP) models are generally too large to be validated or fit in a traditional sense, and they can become intractable to standard methods of analysis or even to the modeler's own intuition. Model reduction can alleviate these issues of complexity by eliminating portions of a system that have minimal effect upon the outputs or time-scales of interest. In this blog post, I'll discuss how this approach can yield simplified models that still provide accurate predictions.

What is quantitative systems pharmacology?

In short, quantitative systems pharmacology seeks to unify the computational modeling of drug disposition with detailed mechanistic descriptions of target-scale dynamics of drug action.

Traditional methods such as pharmacokinetic/pharmacodynamics (PK/PD or pharmacometric) models have their own advantages and disadvantages. Their strengths include their ability to be fit to real world data and often produce simple, highly predictive models. On the downside, they have limited mechanistic explanatory power.

On the other hand, systems biology methods tend to create highly mechanistic models that enable insight into how drug action occurs. But these models are typically too complex to match to data or intuitively understand.

Why invest in QSP?

Both business and scientific rationale have driven investment in QSP. First, complex, multifaceted diseases such as dementia, diabetes, and heart disease are on the rise. For example, the worldwide incidence of dementia is expected to double over the next 30 years. We need more complex and nuanced models to understand these diseases and develop new therapeutics.

In addition, traditional drug development approaches are proving increasingly expensive. "Erooms Law" shows an exponential decline in

the number of drugs developed per billion dollars in research spending since the 1950s. So, we need novel approaches to drug development to revitalize pharma productivity.

Finally, we need a solution to the problem of Phase 2 attrition—the biggest cause of drug program failure over the last 20 years. Incomplete understanding of drug efficacy is a major source of these failures. Therefore, we need to better understand how efficacy emerges from complex biological systems. Because we don't understand the consequences of perturbing these complex systems, we're often not picking the right drug targets. QSP uses mathematical modeling and simulation to unravel the biology behind the systems we seek to manipulate.

What's different about QSP from the perspective of modelers from different backgrounds?

Different types of scientists—systems biologists, pharmacometricians, and mathematical biologists—approach QSP from differing perspectives. For a systems biologist, the key difference is the introduction of drugs into the biological system. In terms of modeling, we're adding on pharmacokinetics and ADME—the absorption, the distribution, the metabolism, and the excretion of the drugs.

For the pharmacometrician, QSP introduces complex, mechanistic descriptions of the target scale dynamics. This adds significant complexity compared to traditional pharmacometric modeling approaches.

And from my perspective as a mathematical biologist, QSP could just mean more differential equations. Large models that stitch together PK and systems biology.

But in fact, the key difference is that QSP models are *controlled.* We are attempting to control a diseased system by administering medication. To the mathematician's mind, this would suggest that they use control theory.

Challenges in QSP modeling

Like any method, QSP models have their own challenges including:

- Parameterization of very large models
- Model validation: what to include in a complex model in terms of target scale dynamics and what to leave out
- Model identifiability
- Model complexity

By seeking to describe target scale dynamics systemically, QSP grapples with model complexity. Other fields such as engineering and computational physics have used model reduction to address this problem.

Defining Model Reduction

Model reduction is any method designed to give a system capable of *satisfactorily reproducing the dynamical behavior of the original model* (under some given metric of error) while *reducing the number of species, reactions, or complexes.*

Model reduction can simplify QSP models and get them to the scale of pharmacometric models. It can also decrease simulation time and ameliorate the problem of parameter identifiability.

The optimal reduction depends upon your specific research questions. Model reduction has the potential to bolster QSP, and I've personally found it to be a useful tool. ■

Author Bios

Behtash Bahador is a Senior Project Manager for the non-profit Center for Information and Study on Clinical Research Participation (CISCRP). With a background in health communication, Behtash leads global implementation of programs for communicating clinical trial results in plain language for a wide range of industry sponsors. He works directly with sponsors to align best practices in patient education and health communication with regulatory and industry guidelines.

Leon Bax is a Director of Consulting Services at Certara Strategic Consulting. He has over 10 years of academic and consulting experience in epidemiological and statistical modeling, with a focus on methodology of mid- and late-phase drug development. He holds two PhDs, one in Clinical Epidemiology and one in Medical Informatics, and is an expert in the field of meta-analysis.

Peter Bonate is Executive Director of Pharmacokinetics, Modeling and Simulation at Astellas and the author of *Be a Model Communicator: And Sell Your Models to Anyone.*

Julie Bullock has over 10 years of drug development experience within the FDA. Dr. Bullock's past appointments include Clinical Pharmacology Team Leader and Senior Clinical Pharmacology Reviewer (FDA). Her regulatory experience was focused in the therapeutic areas of hematology/oncology and coagulation. She has unique insight in pediatric development, PK/PD approaches for biosimilar products, oncology dose finding strategy, and streamlining development for breakthrough therapies and accelerated approval. Dr. Bullock has contributed to over 14 new molecular entity approvals during her FDA career.

Angela Colbers is a biomedical scientist trained at Radboud University Medical Center in Nijmegen, the Netherlands, where she also obtained her PhD in the field of Clinical Pharmacology. Since 1995, she has been involved in clinical trial management, analysis, and reporting. She worked for a pharmaceutical company and contract research organizations. Since 2008, she has worked as a researcher at the department of Pharmacy of the Radboud University Medical Center, which has taken the initiative to set up a network of hospitals investigating pharmacokinetics in pregnancy in Europe. Dr. Colbers is project coordinator of a protocol entitled "Study on Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women (PANNA)." In addition, she teaches and advises PhDs and other students on developing and executing clinical trials, and she supports senior scientists with their research.

Rob Connelly brings a wealth of experience in regulatory operations and electronic publishing to Synchrogenix, a Certara company, having developed a variety of internal systems and overseen the submission of marketing applications to several countries during his nearly 20 years. Mr. Connelly successfully scaled and presided over a growing regulatory operations group at ViroPharma and fulfilled a variety of roles in regulatory operations at GlaxoSmithKline. His expertise includes evaluating and working with dozens of publishing, tracking, and document management systems and customizing those solutions to function efficiently within the parameters set forth by individual organizations with unique environments. In his role as Product Manager for GlobalSubmit Electronic Submissions Software, Mr. Connelly applies the insights gleaned working from a regulatory vantage point to developing software tools that result in greater quality and streamlined processes for the life science industry. Mr. Connelly received both his BS in Finance and MBA from La Salle University in Philadelphia, PA.

Iain Gardner has been at Certara since 2011. He leads the science team that is responsible for further developments of the population-based physiologically-based PK/PD Simulators to meet the needs of our consortium members.

Ronette Gehring is an associate professor of clinical pharmacology at the Kansas State University College of Veterinary Medicine, where she directs the Midwest Regional Center of the Food Animal Residue Avoidance Databank (FARAD). Her research interests lie with using computer-based modeling as a quantitative framework that integrates and explains pharmacokinetic and pharmacodynamic data based on current scientific understanding in veterinary and comparative pharmacology.

Oliver Hatley is a research scientist who has been working at Certara since 2013. He obtained his PhD investigating *in vitro-in vivo* extrapolation of intestinal metabolism from the Centre for Applied Pharmacokinetic Research (CAPKR) at the University of Manchester. Oliver is part of the translational sciences in DMPK group within Simcyp and has lead development of the esterase organ and blood *in vitro-in vivo* scaling strategies. He is also involved in the development of special populations within the Simcyp Population-based Simulator.

Shuhua Hu is a senior research scientist in the scientific group at Certara. Before joining Certara, she worked at North Carolina State University for ten years with a research focus on mathematical modeling, simulation, estimation, optimal control, and uncertainty propagation and quantification in the area of biomedicine and engineering. She has published over 30 peer-reviewed journal publications and a book, *Modeling and Inverse Problems in the Presence of Uncertainty.*

Alice Ke obtained her PhD in pharmaceutics from the University of Washington, Seattle, where her research was focused on the assessment of fetal and CNS drug distribution using clinical imaging techniques. She then accepted an ORISE fellowship in the Office of Clinical Pharmacology at the FDA, where she developed and validated PBPK and population PK models to support dose adjustments for pregnant women. After completing her fellowship, Dr. Ke was a research scientist in the Department of Drug Disposition and PK/PD at Lilly Research Laboratories, where she applied population PK and PBPK modeling & simulation techniques to provide model-based advice on the design of clinical pharmacology studies. Currently, Dr. Alice Ke is a Consultant and Scientific Advisor at Certara. Her research interests continue to center around the applications of PBPK and PK/PD modeling to predicting complex drug interactions and PK/PD in special populations.

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.

Lora Killian, Director of Transparency and Disclosure at Synchrogenix, a Certara company, has over 12 years of pharmaceutical and business operations experience. She is responsible for the development and oversight of Synchrogenix's entire suite of transparency services which includes anonymization, clinical trial disclosure, and lay language summary development. Ms. Killian has played an integral role consulting with sponsors in the development of company-specific transparency policies to address the latest wave of regulation arising out of the EU and the US.

Ellen Leinfuss brings more than 25 years of experience leading marketing, business development, and sales management groups for technical and scientific-based organizations. She spent the last 9 years at UL EduNeering, a global provider of regulatory compliance educational solutions delivered via cloud-based technology. At UL, Ms. 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 and its exclusive partnerships with AdvaMed and the Personal Care Products Council, among others. Ms. 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.

Barry Mangum, Founder and CEO of Paidion Research, is responsible for their vision of profound and meaningful change in global pediatric clinical research. Paidion is catalyzing change in an old paradigm and laying the groundwork for developing safe and effective medicines for children. Responsible for partnering with clients to implement clinical trials for all phases of pediatric drug development, Dr. Mangum brings decades of pediatric clinical research expertise to Paidion. His extensive academic experience includes serving as faculty and researcher in pediatrics and clinical pharmacology/pharmacotherapy at Duke's and UNC's medical schools. His corporate experience includes serving as Senior Director of Pediatric Clinical Development Services at Quintiles. He has numerous publications, presentations, and memberships, including co-authorship of *NeoFax: A Manual of Drugs Used in Neonatal Care,* the leading guide for dosing neonatal medications in the US, as well as the NeoFax software package and mobile device app.

Suzanne Minton is the scientific communications manager at Certara. Dr. Minton helps develop the science-focused, value-oriented content that our customers go wild for. When she's not writing about the hottest problems in drug development, Suzanne enjoys spending time with her husband and two young children.

Shriram Pathak has been a Senior Research Scientist at Certara since 2013. He is part of the modeling and simulation group and is involved in development and improvement of absorption and bioavailability models implemented within the Simcyp Population-based Simulator. He is also involved in the development of tools for mechanistic modeling of biopharmaceutical *in vitro* experiments that can be used to inform *in vivo* modeling within the PBPK framework. Shriram's main research interests include biopharmaceutics, pharmacokinetics, and modeling and simulation of oral drug delivery systems.

Maria Saluta obtained her BS, MS, and PhD in Microbiology from St. John's University. Maria has held various research, scientist applications support, and leadership roles in the life sciences and diagnostics industries, and is currently the Sr. Product Marketing Manager for modeling and simulation at Certara. In her spare time, she loves to experience the earth and its inhabitants by globetrotting to off-the-beaten path destinations.

Graham Scott, Senior Director, Clinical Pharmacology, Certara Consulting Services, has more than 30 years of 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.

Steven Sibley is the Vice President of Global Submissions and Submission Leadership at Synchrogenix, a Certara company. With a career spanning more than 20 years in the pharmaceutical industry, Mr. Sibley has extensive regulatory and writing experience, preparing a wide variety of both non-clinical and clinical documents and leading project and submission teams.

Tom Snowden received his PhD in applied mathematics and quantitative systems pharmacology from the University of Reading in 2015. He was then awarded and completed an EPSRC doctoral prize fellowship at the university, continuing his research at the interface of mathematics and pharmacology. In October 2016, Tom joined Certara QSP as a research scientist working on a range of QSP consultancy projects.

Stacey Tannenbaum is Senior Director of Modeling and Simulation at Astellas and co-founder of the American Conference on Pharmacometrics (ACoP) and the International Society of Pharmacometrics (ISoP).

Nathan Teuscher is a Vice President of consulting services at Certara. He is an expert in clinical pharmacology, pharmacometrics, pharmacokinetics and pharmacodynamics and was trained by David Smith at the University of Michigan. Dr. Teuscher has held leadership positions in biotechnology, pharmaceutical and contract research companies. In 2008, he established the Learn PKPD.com website to share his knowledge with the community. Prior to coming to Certara, he was the Founder and President of PK/PD Associates.

David Turner is a principal scientist at Certara's Simcyp division.

Nirpal Singh Virdee comes with over 18 years of life sciences experience. He is a subject matter expert in the clinical development, regulatory landscape, transparency and disclosure space. He is considered an industry thought leader, having globally presented at conferences. He has sat on industry advisory panels. At Synchrogenix, a Certara company, Nirpal is accountable for business development, client management, and consulting for technology-enabled services.

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.

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