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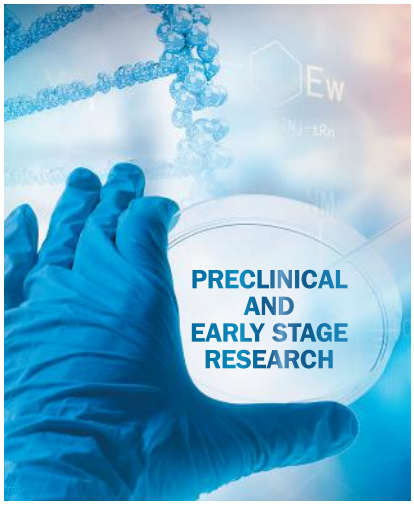

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Leveraging Biosimulation for Pediatric Drug Development

J.F. Marier, Trevor N. Johnson, Suzanne Minton

Pediatric trials now feature increased modeling and analytics for safer drug dosing and response.

Historically, most medications given to children had not been evaluated in pediatric clinical trials due to logistical and ethical challenges. Indeed, while children represent about 40% of the world's population, only 10% of the drugs on the market have been approved for pediatrics.[1] Without a proper and approved clinical process, physicians are left with potentially unsafe dosing and therapeutic approaches for children. The result is a continuation of the off-label prescribing.

To address this urgent medical need, both the FDA and the 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. The combination of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) and these new regulatory requirements are starting to move the pendulum towards safer, more effective medicines for children. During the five-year period between 2007 and 2013, 469 pediatric studies were completed under BPCA and PREA; by August 2014, 526 labeling changes were made.[2] Similarly, in the European Union, around 300 products have had label changes approved for safety, efficacy, or dosing for pediatrics since 2007.[2]

While these requirements have spurred growth in pediatric clinical research, there are still major barriers to successful pediatric drug development. Almost half of the trials conducted in recent years have failed to demonstrate either safety or efficacy. A total of 44 products had failed pediatric drug development trials submitted to the FDA between 2007 and 2014.[3] An analysis by Gilbert J. Burckart, PharmD, and his FDA colleagues revealed several common factors that contributed to the widespread failures: suboptimal dosing, differences between adult and pediatric disease processes, and problematic study designs.

In the cases where suboptimal dosing contributed to the failure to show efficacy, there were two frequent issues: not testing a range of doses, and limiting pediatric drug exposure to that which was shown to be efficacious in adults. Testing a range of doses is critical to understanding dose-response relationships for a drug. Also, if the disease process differs between children and adults, then matching the drug exposure to that observed in adults may not be effective, and ultimately result in clinical trial failure.

An understanding of pediatric disease—its natural progression—is crucial for selecting outcomes for clinical studies, including the primary efficacy endpoint, safety, and biomarkers. Finally, problematic study designs are a significant contributing factor in clinical trial failures. Some of these issues included lack of a control group, stratification, and inadequate assay sensitivity.

A biosimulation framework to support strategic decision-making

First, it's important to clarify some definitions regarding pediatric age groupings. According to the FDA guidance, neonates are from birth to one


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month, infants are from one month to less than two years of age, children are from two to 11 years old, and adolescents are from 12 to 18 years old. As pharmacokinetics (PK) and pharmacodynamics (PD) may change between each age range, drug developers may need to develop dosing regimens specific to each subgroup.[5]

The very nature of human growth and maturation makes the prediction of PK in children especially challenging. Drug disposition in children differs from that of adults in numerous ways. For example, the kinetics of drug absorption may be different in children versus adults due to changes in the expression of intestinal drug transporters and drug metabolizing enzymes during development.[4] Likewise, drug distribution changes with age as neonates (birth up to one month) have much higher total body water compared to adults. Finally, organ maturation has a significant effect on drug metabolism and excretion. Children have relatively larger livers, lower glomerular filtration rates, and less renal tubular absorption and excretion compared to adults.[6] This distinct physiology means that traditional approaches such as allometry risk greatly over or under predicting drug clearance in pediatric patients, especially those that are less than one year old.[7]

Because of the special needs of children as well as ethical concerns, there are significant differences in clinical trial protocols for children versus those for adults. The FDA guidance document discusses these issues at length.[5] Some of the major issues in pediatric clinical studies include the following:

- The type of PK study that is possible is often different in adults and children. While rich sampling is often conducted in adults, a sparse sampling procedure is generally preferred for young children to minimize the number and volume of blood draws.
- When studying neonates, sponsors may need to consider gestational as well as postnatal age when determining covariates for a population PK study.
- The formulation of a drug may change between age groups. Young children generally cannot swallow pills and may require liquid formulations.

How can pediatric drug developers satisfy regulatory requirements and maximize drug safety and effectiveness while minimizing children's exposure to experimental medications? Biosimulation—also known as model-based drug development—includes both empirical "top down" PK/PD modeling and simulation as well as "bottom up" physiologically-based pharmacokinetic (PBPK) models. It leverages prior information from preclinical studies, adult

trials, peer-reviewed literature, and pediatric studies of related indications or drug actions. The integration of patient physiology, drug actions, and trial characteristics in models enables sponsors to optimize dosing and trial design. Indeed, in a study of 11 well characterized drugs, PBPK models of virtual subjects (birth to 18 years of age) showed greater accuracy in predicting drug clearance than simple allometry, especially in children less than two years of age.[8] The increased certainty in biosimulated outcomes can help sponsors to ensure informative pediatric trials are performed and will gain approvals based on a smaller number of pediatric patients.[9]

Population PK and PBPK models based on Phase I data from adults are frequently used to develop a drug model that aids with pediatric dose selection.

Opportunities during drug development for applying modeling and simulation techniques

As the benefits of biosimulation become increasingly clear, regulatory agencies are also advocating its use to improve the success rate of pediatric trials from current levels.[10] Indeed, a 2014 draft guidance from the FDA states that "modeling and simulation using all of the information available should, therefore, be an integral part of all pediatric development programs."[5]

At each stage of clinical development, there are specific trigger points and opportunities to apply modeling and simulation techniques to increase the likelihood of success. Submission of the PIP is required by the EMA by the end of Phase I clinical studies. Biosimulation methods should be used to support the dosing rationale stated in the PIP. Population PK and PBPK models based on Phase I data from adults are frequently used to develop a drug model that aids with pediatric dose selection. Population PK or PBPK models can predict drug exposure across a wide range of ages and weights as well as maturation and organ function. The predicted drug exposure in pediatric patients can then be compared against observed values in adult subjects in Phase I to confirm the models and optimize the safety of treatments. This approach can also be used to develop a sparse sampling strategy that optimizes the assessment of PK parameters while minimizing the number of blood draws and other invasive procedures. Pediatric PBPK and population PK models can be used synergistically during drug development. The former have recently been used to aid in the determination of optimal dose and sampling times for population PK.[11] Conversely, the results from population PK models can be used to further optimize pediatric PBPK models.

Another important use for PBPK models in pediatric drug development is evaluating the risk of drug-drug interactions (DDIs). DDIs are a primary threat to the safety and efficacy of clinical practice. Clinically-relevant drug interactions are primarily due to drug-induced alterations in the activity and quantity of metabolic enzymes and transporters. Indeed, DDIs that cause unmanageable, severe adverse effects have led to restrictions in clinical use, and even drug withdrawals from the market.

The magnitude of any DDI depends on the fractional importance of the inhibited metabolic pathway. The pattern of CYP metabolic enzymes that contribute to the elimination of a drug may not necessarily be the same in children compared to adults. Thus, it is difficult to use information about DDIs in adults to inform the likelihood of pediatric DDIs. And, again, there are practical and ethical problems with evaluating DDIs in pediatric clinical studies. A 2012 guidance from the EMA states that PBPK simulations may be used to predict the effects of drug interactions in multiple special populations, including young pediatric patients.[12]

Use of the Simcyp Pediatric Simulator to simulate DDIs revealed that in certain scenarios, neonates could be more sensitive to a DDI than adults while the opposite might be true in other scenarios involving different CYP enzymes.[13] Pediatric PBPK models may help provide information about the risk and magnitude of potential DDIs where there are no existing clinical data.

Pharmacometrics tools are also invaluable in supporting pediatric study plans. The PSP should be submitted to the FDA at the end of the Phase II meeting, following the availability of exposure-response data in adults. To provide guidance on the conduct of pediatric trials, the FDA has articulated a pediatric study decision tree.[14] The degree of similarity of disease progression and drug response between adults and children determines which of three major pediatric studies should be undertaken: PK only, PK/PD, PK, or efficacy. Safety studies are required in all of these scenarios.

The regulatory path taken determines the strategy for optimizing dosing. In the case that PK studies alone are used, the sponsor should build a population PK model customized for size and maturation and perform dose simulations that will result in drug concentrations within the range of those observed in adults. Using the PK/PD approach means creating a population PK/PD model that is customized for size and maturation and performing dose simulations that will achieve a target concentration based on the PK/PD relationship. Finally, utilizing a PK and efficacy approach involves building a population PK model and an exposure-response model, and performing simulations to find a dose that will produce a drug concentration that results in an adequate response.

Phase III studies in adults are performed to determine whether there is statistically-significant evidence of clinical efficacy and safety for an investigational drug. At this

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point, the PIP and PSP should be updated to reflect any new insights. This is also the time to develop final pediatric protocols. Clinical trial simulations using Phase II results can be useful for evaluating probability of success in Phase III.

The PSP should be submitted to the FDA at the end of the Phase II meeting, following the availability of exposure-response data in adults.

Two case studies showing successful use of biosimulation for pediatric drug development

Learning from one indication to the next: Eculizumab for atypical hemolytic uremic syndrome

In some cases, information gained developing a drug for one indication can be leveraged to inform its approval for a different indication. PNH (paroxysmal nocturnal hemoglobinuria) is a rare, progressive, and life-threatening disease. It is characterized by rampant destruction of red blood cells (hemolysis) and excessive blood clotting.[15] Likewise, aHUS (atypical hemolytic uremic syndrome) is an ultra-rare genetic disease that causes abnormal blood clots to form in small blood vessels throughout the body. The sequelae of aHUS include kidney failure, damage to other organs, and premature death. There were no FDA-approved treatments for this rare disease.

Both aHUS and PNH are caused by chronic, uncontrolled activation of the complement system. During activation of the complement system, the terminal protein C5 is cleaved to C5a and C5b. C5a and C5b have been implicated in causing the terminal complement-mediated events that are characteristic of both aHUS and PNH. Eculizumab is a humanized monoclonal antibody (mAb) that binds C5, thereby inhibiting its cleavage. In 2007, this mAb received approval for treatment of PNH based on evidence of effectiveness from clinical studies.[16]

To help the sponsor obtain accelerated approval of eculizumab for the treatment of aHUS in both adults and pediatric patients, Certara scientists leveraged previous knowledge gained during its development for PNH. Their starting point was a population PK model that had been previously constructed in adult patients with PNH.[17] This model was customized and used to develop optimal dosing strategies for adult and pediatric aHUS patients.

Comparing the case of adults with PNH to pediatric aHUS, it became apparent that children have a different response to intervention and that a different endpoint should be used. The PK/PD relationship in PNH was leveraged to measure the drug's exposure and inform pediatric dosing for aHUS. Knowledge about eculizumab's mechanism of action for PNH also suggested that optimal binding to the pharmacological target (C5) should translate into a clinical benefit.

Identification of the therapeutic dosing window for a mAb in pediatric patients with a rare disease involved several steps. First, to ensure patient safety, the upper exposure limit needed to be determined. As a safeguard against toxicity, the upper exposure limit was capped at what had been previously observed in adults. To ensure efficacy, the minimum drug exposure also had to be determined. Using the predicted concentration of the soluble target and the binding characteristics of the mAb to its target, a minimum concentration threshold was set to obtain close to full inhibition of the target. Then, trial simulations using a population PK model were performed to determine which doses would optimize the probability of obtaining the mAb within the window of target engagement. This enabled the dosing recommendations to be determined for pediatric patients of varying weights.[17]

The clinical program for aHUS involved two Phase II studies and a retrospective observational study. A total of 57 patients with aHUS participated in these studies (35 adult, 22 pediatric patients). Two different biomarkers were used to assess the efficacy of treatment. The proximal biomarker, free C5, showed complete suppression upon treatment with the mAb. Likewise, the mAb caused full inhibition of hemolytic activity (the distal biomarker).[17] The primary endpoint indicated that the response to the intervention exceeded 95%. Patients treated with the mAb experienced several benefits, including higher improvement in platelet counts and other blood parameters and better kidney function, even eliminating the requirement for dialysis in some patients. Soliris® (eculizumab) received FDA approval to treat aHUS patients in 2011.[18]

Using PBPK modeling to assess differing drug formulations for pediatric patients

Quetiapine is an atypical antipsychotic drug for the treatment of schizophrenia, bipolar disorder, major depressive disorder, and generalized anxiety disorder. An immediate release (IR) formulation of quetiapine was first approved by the FDA in 1997 and has been extensively studied in adults, children, and adolescents. Regulatory approval for the extended release (XR) formulation was granted for use in adults, with the requirement that pediatric studies must be carried out for children over the age of 12.

Various factors influence the bioavailability of different formulations, including the release of the active ingredient, its dissolution and permeability across the GI tract, as well as intestinal metabolism. Furthermore, alterations in PK in children can be due to differences in absorption and transit rate, organ size, blood flow, tissue composition, and metabolic capacity at various developmental stages. The

challenge was to integrate the available *in vitro* ADME, physiochemical, and clinical data into PBPK models to predict the effects of age and formulation on the PK of quetiapine in young subjects.

Scientists at Certara and AstraZeneca developed PBPK models that predicted, with reasonable accuracy, the effects of CYP3A4 inhibition and induction on the PK of quetiapine, the PK profile of quetiapine IR in both children and adults, and the PK profile of quetiapine XR in adults. These validated models were then used to simulate relative exposure following XR formulation in adolescents (age 13-17) and children (age 10-12). In both groups, the predicted exposure to quetiapine XR followed a similar pattern to the IR formulation, with 300mg XR once-daily being comparable with 150mg IR twice-a-day.[19]

Conclusion

The high rate of trial failures, increasing regulatory demands, and ethical imperatives all require a reexamination of the current approach to pediatric drug development. Biosimulation is a proven approach that will help optimize trial design and inform the drug label. This approach can support global regulatory strategies that increase the likelihood of success for pediatric drug development programs.

J.F. Marier, PhD, is Vice President and Lead Scientist; Trevor N. Johnson, PhD, is Principal Scientist; Suzanne Minton, PhD, is Manager of Scientific Communications; all with Certara

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Modeling and Simulation in Trials: Potential or Hype?

Sujay Jadhav

The use of computer-based biosimulations to aid drug development has grown, but adoption hurdles remain.

Improving experimental drug success rate[1] and accelerating clinical development[2] are top priorities for pharmaceutical companies. Careful decision-making during drug development is essential to minimize development time, manage costs and improve the probability of commercial success. Recently, many of the major pharmaceutical companies have begun to explore computer-based biosimulation strategies to help generate the information necessary to make better decisions.[3,4] These strategies go by many different names—clinical trial simulation (CTS), modeling and simulation (M&S), computer-assisted trial design (CATD), model-based drug development (MBDD), and model-informed drug discovery and development (MID3). The FDA and European Medicines Agency (EMA) have also taken notice of M&S strategies in an effort to support improved drug development efficiencies.

Computer-based modeling and simulation has already had a beneficial impact on many different fields and industries—physics, chemistry, aeronautics, meteorology, material science, finance, and musical composition.

In finance, for example, professional investors traditionally work to find a handful of undervalued companies in which to invest, a process which typically involves interviewing management teams, researching corporate strategies, and analyzing demand for products and services. Artificial intelligence is changing all of that. Quantitative-investment, or "quant," funds, rely on high-speed computers and trading models that evaluate publicly available data to make investment decisions—without ever talking to management teams. Today, one quant fund named Two Sigma is the fastest growing hedge fund on Wall Street, which manages over $35 billion in assets.

Despite its promise, adoption of M&S in the pharmaceutical industry has lagged due to the complexity of modeling biological systems, insufficient scientific understanding of disease conditions, and lack of large amounts of real-world health outcome population data. Significant progress in these areas has occurred over the last decade, and M&S is now being promoted as having the potential to transform the drug development process from R&D all the way to commercialization and life-cycle management. The prevailing question amid all the momentum: is this potential real or just hype?

What is modeling and simulation?

With regards to the drug development process, M&S involves modeling compounds, mechanisms and disease level data based on historical observations. Computer simulations are run on these models to generate information that can be used to predict outcomes, thereby improving the quality, efficiency and cost-effectiveness of decision-making.

For clinical trials, specifically, a CTS would attempt to study the effects of a drug in a virtual patient population using mathematical models that

incorporate information on physiological systems. Simulations can be used to test assumptions, improve predictability, better characterize risk and identify opportunities to optimize outcomes by observing the effects of different model inputs. An understanding of the full range of potential outcomes can be cultivated by observing the effects of more extreme model inputs than have been observed in real-world patients, for example. In this way, M&S can help investigators better plan and design clinical trials by exploring and quantifying risks prior to the start of studies.

> **M&S is now being promoted as having the potential to transform the drug development process from R&D all the way to commercialization and life-cycle management.**

Examples of modeling and simulation

Efficacy and safety issues are of the upmost importance in clinical trials—either the substance in question does not have sufficient biological activity, or it does not have manageable toxicity. But the level of efficacy or toxicity in a drug is very much related to the dose level and schedule used. Poor dose and scheduling choices can have serious consequences for drug safety and efficacy in a clinical trial; resulting late-stage failures, or registration delays as problems must be investigated and corrected. As a result, determining the proper dose and scheduling of a drug prior to the start of a clinical trial is extremely important in order to avoid a preventable failure.

The most mature application of M&S in clinical trials is pharmacokinetic (PK) modeling for dose and scheduling determination. This M&S application has been successful in predicting optimal dosing regimens from preclinical to Phase III studies.[5] By understanding patterns in the exposure-response relationship, population PK/pharmacodynamics (PD) analysis can also help to identify dose adjustments needed for special populations—children, the elderly, ethnic groups, patients with impaired renal/hepatic function, and patients likely to experience drug-drug interactions.[6,7]

Other uses for CTS may include answering those questions that can be difficult or impractical to answer using clinical trial methods. When the American Diabetes Association wanted to compare the effectiveness of current diabetes management approaches, for example, Archimedes Inc. simulated a 30-year clinical trial using a physiology-based model to predict outcomes in a patient population.[8] Physiology-based models strive to model disease processes at a biological level using equations that are calibrated with data from empirical sources. When properly constructed, these models can be used to identify priorities in clinical trials, facilitate design of new trials, or enable the conduct of virtual comparative effectiveness trials.

M&S also appears to have value in optimizing study design.[9] The idea is to increase the efficiency of clinical trials by establishing appropriate trial size and collecting relevant data at optimal times to generate knowledge. Simulations are used to explore different clinical study designs to select the best option.

Use of M&S in clinical trials seems to have a dramatic impact on FDA approval and labeling decisions. A 2011 review conducted by the FDA found a dramatic increase in both the number of reviews with pharmacometric analysis and the impact of those analyses on drug approval and labeling decisions. Pharmacometric analysis was found to have made an important contribution to 126 drug approval decisions (64%) between the years 2000 and 2008. Additionally, pharmacometric analysis was found to impact labeling decisions in 133 applications (67%) during this time period.[10] Finally, in the midst of an influenza epidemic in 2009, the FDA used M&S to identify and approve a safe pediatric dose of an experimental drug, peramivir, that had never been studied in children.

Modeling and simulation throughout the drug development process

The pharmaceutical industry is slowly beginning to adopt M&S across many different aspects of the drug development process. One example is the use of M&S to assess structure-affinity relationships of experimental drug compounds to predict toxicity and safety.[11] Results of these kind of simulations are increasingly being utilized by regulatory agencies. Another example is the use of M&S to predict the overall cost-effectiveness of new medicines in the health technology assessment process.[12] M&S is also being used to provide for more effectively management of a biopharma company's R&D development portfolio.[13]

The opportunities for cost and time savings in the drug development process by utilizing M&S are enormous. This economic incentive is being supported by the rapid growth of computational power and patient health data, along with advances in scientific understanding. Because of this "perfect-storm" combination of factors, scientists are starting to utilize M&S to tackle some of medicine's toughest "what-if" questions, and new applications for M&S throughout the drug development process are being discovered rapidly.

Conclusion

While adoption of M&S by the pharmaceutical industry has been slower than in other industries, recent years have seen M&S utilized in all phases of the drug development process.

M&S practices support knowledge-based approaches that can make drug development processes more efficient and informative, thereby enhancing return on investment for drug developers in today's challenging business environment. M&S offers drug developers in pharmaceutical companies the opportunity to quantify problems, test assumptions, increase predictability, improve decision-making, and ultimately lower costs.

Because of this perfect-storm combination of factors, scientists are starting to utilize M&S to tackle some of medicine's toughest "what-if" questions.

As advances in computational power, patient health data, and scientific understanding continue to grow, M&S will likely play a larger role in the development of life-saving medicines —in terms of supporting both pharmaceutical company internal decision-making and applications for regulatory approval. Increased reliance on M&S will lead to new, more collaborative ways of working, as experts from diverse fields will be required to come together to frame the questions and quantify assumptions for simulations. Ultimately, these collaborative efforts will serve to improve the drug development process, leading to better medicines delivered to patients in a timelier fashion.

Sujay Jadhav is the CEO of goBalto

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EMA Progresses on First-in-human Trials Guideline

The agency is finalizing its anticipated guidance update on early clinical development strategies

The European Medicines Agency (EMA) is moving ahead with its plan to revise the guideline on first-in-human clinical trials.

According to a statement issued by the agency on May 24, "The revised guideline is now being finalized. It will be adopted by the Committee for Medicinal Products for Human Use (CHMP) and then published on the EMA website in the third quarter of 2017."

> **"The revised guideline will be adopted by the Committee for Medicinal Products for Human Use (CHMP) and then published on the EMA website in the third quarter."**

EMA published a revision of its guideline on first-in-human clinical trials for public consultation in November 2016. The consultation closed on February 28 and a month later, EMA ran a workshop with regulatory agencies, the pharmaceutical industry, contract research organizations (CROs), and academia to discuss the comments received.

The aim of the workshop was to finalize the guidance with the further involvement of stakeholders. It focused on discussing the comments received during the consultation phase, and participation was limited to those individuals and organizations who submitted comments. The output of the workshop will be reflected in the final revised guideline and the published

overview of comments, according to the EMA.

The existing guideline, released in 2007, provides advice on first-in-human clinical trials, particularly on the data needed to enable their appropriate design and allow initiation of treatment in trial participants. Between July and September 2016, EMA released for public consultation a concept paper that outlined the major areas that needed to be revised in the guideline, and the draft revised guideline was then adopted by the CHMP.

> **"The revised guideline is designed to address the increasing complexity of protocols of first-in-human clinical trials in recent years. The practice for conducting these trials has evolved toward a more integrated approach."**

The revised guideline is designed to address the increasing complexity of protocols of first-in-human clinical trials in recent years. While the 2007 guideline focused on the single-ascending-dose design used at that time, the practice for conducting first-in-human clinical trials has evolved toward a more integrated approach, EMA explained. Sponsors now conduct several steps of clinical development within a single clinical trial protocol (e.g., to assess single and multiple ascending doses, food interactions, or different age groups).

The authors of the guideline have outlined strategies to mitigate and manage risks for trial participants, including principles to be used for the calculation of the starting dose in humans, the subsequent dose escalation, and the criteria for maximum dose, as well as principles on the conduct of the clinical trial including the conduct of studies with multiple parts. They have also covered non-clinical aspects such as the better integration of pharmacokinetic (PK) and pharmacodynamic data (PD) and toxicological testing into the overall risk assessment, as well as the role of non-clinical data in the definition of the estimated therapeutic dose, maximal dose, and dose steps and intervals.

"Guidance is also provided on clinical aspects, including criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level," the authors noted.

Philip Ward is *Applied Clinical Trials'* European Editor

THE SCOPE of EMA's revision of the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products"

- Covers non-clinical and quality issues for consideration prior to the first administration in 105 humans and the design and conduct of clinical trials (CTs) that generate first knowledge in humans during early clinical development.
- Early phase CTs include, in this guideline, those which generate initial knowledge in humans on tolerability, safety, pharmacokinetic (PK) and pharmacodynamic (PD) after single ascending dose (SAD) or multiple ascending dose (MAD).
- These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations.
- The guideline applies to all new chemical and biological investigational medicinal products (IMPs). While many of the scientific principles included apply to advanced therapy IMPs as well, these products are not included in the scope of this guideline.

View the full guidance here: http://bit.ly/2faQusB

Photo courtesy of EMA

The EMA head office in Canary Wharf, London.

Accenture, BioCelerate Collaborate on Preclinical Platform

Accenture, a professional services strategy and technology company, recently revealed it will work with BioCelerate, a subsidiary of TransCelerate BioPharma Inc., a nonprofit focused on improving efficiencies in R&D, to develop a platform enabling BioCelerate member companies to aggregate and analyze preclinical and clinical information to improve drug development efficiency and accelerate medicines to the market.

"The ability to collect and leverage large amounts of precompetitive information to create new insights in the R&D process is an important development in the preclinical research space," said Kevin Julian, senior managing director, Accenture Life Sciences North America and Accelerated R&D Services. "We are eager to collaborate with BioCelerate on this critical initiative to further enable the sharing of data to maximize the value of preclinical and clinical research and deliver better patient outcomes."

The R&D data sharing platform will be built on the Accenture Insights Platform. This platform provides a portfolio of advanced analytics capabilities, and an integrated design, build, and run environment, to enable the development of industry and function-specific analytics solutions.

The platform will provide BioCelerate members the ability to assimilate, aggregate, and analyze de-identified preclinical and clinical information, enabling them to draw their respective conclusions from a large data set. The platform will be used initially to support BioCelerate's first collaborative project, Toxicology & Background Control Data Sharing, to enhance product safety.

"Sharing preclinical data among the BioCelerate member companies can be a powerful tool for improving drug discovery and development. With this initiative, BioCelerate members will be able to make more informed decisions on compound progression based on a better understanding of preclinical safety data," said Dr. Mike Graziano, vice president of drug safety evaluation at Bristol-Myers Squibb and lead for the BioCelerate initiative.

Dr. Dalvir Gill, CEO of TransCelerate, said, "Accenture's deep expertise in life sciences, digital, analytics, and clinical data-related services will be instrumental in delivering this new platform and builds on the multi-year relationship between Accenture and TransCelerate. All BioCelerate member companies signed a collaborative data sharing agreement outlining the guidelines of the data that will be shared across companies. This, along with selecting Accenture to build and host the global data sharing platform, marks another significant milestone in advancing the industry. We are truly excited for the long-term strategic vision of this platform and envision a future whereby drug developers can connect preclinical, clinical and other data types within the same data sharing platform."

Following launch of the platform, data from TransCelerate's Placebo Standard of Care Data Sharing (PSoC) initiative will be migrated, creating the foundation for additional preclinical and clinical data sharing across member companies. The PSoC initiative was established to maximize the value of historic clinical data collected during clinical trials, and was the first cross-therapeutic, multi-sponsor clinical data sharing program of its kind designed to improve trial design and safety surveillance.

In October 2015, Accenture was selected by TransCelerate to support its PSoC initiative, which has converted data for over 80 trials and more than 67,000 patients across seven therapeutic areas, such as Alzheimer's disease, cardiovascular disease and diabetes.

TransCelerate and FDA/NIH Partner on Protocol Template

Reinforces the need for harmonized protocol formats

TransCelerate BioPharma Inc. has announced the availability of an enhanced technology-enabled Common Protocol Template (CPT). This update to the CPT, unveiled in May, is in alignment with the common protocol template launched by the FDA and National Institutes of Health (NIH). View here: http://bit.ly/1N4bIoY. This collaborative effort reinforces the need for harmonized protocol formats and content that aligns objectives and endpoints with accepted data standards.

Dr. Dalvir Gill, CEO of TransCelerate, noted, "This milestone represents TransCelerate's continued focus on innovation, process efficiency and partnership, as well as our goal of simplifying clinical trials. This aligned CPT effort could not have come to fruition without the strong collaboration of the FDA and NIH. We will continue to work with our partners, including the Clinical Data Interchange Standards Consortium (CDISC), to develop an automated solution that facilitates the use of data standards required for protocol endpoints."

Since 2010, the number of new studies registered in ClinicalTrials.gov has increased by approximately 20,000 per

year. This includes studies sponsored by pharmaceutical companies, academic centers, contract research organizations (CROs) and members of the NIH, among others. Despite this diversity in clinical research, the protocols that must be developed rely on the same regulatory infrastructure for design, review and implementation. This long-felt unmet need led TransCelerate, in conjunction with the FDA and NIH, to recognize a significant opportunity for improved quality and a reduction in complexity through a closely aligned, common protocol effort.

"The FDA and NIH see protocol harmonization as an essential component to the accelerated delivery of medicines to patients," said Dr. Janet Woodcock, director of the FDA's Center of Drug Evaluation and Research (CDER). "Having aligned templates will help enable health authorities to receive consistent, high-quality protocols, enable timely review and ultimately ensure trial participant safety."

"Recent data indicates that 66 percent of protocols are amended and one-out-of-ten of these protocols are related to human error. The CPT Initiative has worked to decrease protocol-related issues frequently reported by trial sponsors, investigator sites, regulators and patients by creating common content that can be used by any stakeholder such as a health authority or investigational review board," said Dr. Rob DiCicco, vice president, clinical innovation and digital platforms for GlaxoSmithKline, and TransCelerate CPT Initiative leader.

DiCicco goes on to note, "We are hopeful that the intentional connectivity between objectives and endpoints, as well as future connectivity with study procedures, will enable reviewers and other key stakeholders to promptly identify disconnects and unnecessary complexity that often accompany today's industry sponsored protocol."

The template created by the FDA and NIH was developed with single-center NIH sponsored trials in mind, while the TransCelerate CPT includes additional text to support global, multicenter trials and supports re-use of protocol-level information for other requirements of clinical trials, such as statistical analysis plans and clinical trials registry posting.

"Recent data indicates that 66 percent of protocols are amended and one-out-of-ten of these protocols are related to human error."

About the TransCelerate CPT initiative

The TransCelerate CPT Initiative aims to reduce complexity in clinical trial protocols by making implementation and reporting less difficult for sponsors, sites, regulators and, most importantly, patients. The creation of the CPT enables industry trial sponsors, working with other stakeholders, to standardize the format of trial protocols and to develop standards for required protocol endpoints, in alignment with the TransCelerate Clinical Data Standards Initiative. Last year, TransCelerate launched a technology-enabled edition of its CPT, which enabled automated re-use of information and point and click population of selected template sections, among other features. The CPT templates, libraries containing common and suggested text pertinent to certain studies and implementation toolkit materials are accessible to the public through the TransCelerate website.

The TransCelerate CPT Initiative, coupled with the work done by the FDA/NIH has the potential to minimize confusion for stakeholders and allow benefits such as site simplified study start-up and execution, as well as faster review time by health authorities. Other potential benefits include:

- **Investigator sites:** Improved access to streamlined information within protocols; increased consistency between sponsor protocols and reduced need for additional workflow documentation.
- **Institutional review boards:** Enhanced review of data which can allow for easier submission review and potential for a faster approval.
- **Health authorities:** Streamlined protocols should be easier to review, and allow for an increased ease of data interpretation and improved ability to compare clinical trial protocols. The TransCelerate Template introduces data standards in its endpoint sections and the use of controlled terminology permits automated re-use and introduces the concept of traceability.
- **Patients:** Improved communication with investigator sites due to increased consistency between protocols.
- **Clinical trial sponsors:** Increased operational efficiencies in the creation of clinical trial protocols, automation of downstream processes and improved re-use of content, improved conduct of the study and quality of data collected.

The founding members of TransCelerate are AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Co., GSK, Johnson & Johnson, Pfizer, the Roche Group, and Sanofi. Companies that have joined since the group's inception include Allergan Inc., Amgen, Astellas Pharma Inc., EMD Serono Inc. (a subsidiary of Merck KGaA, Darmstadt, Germany), Merck & Co., Novo Nordisk, Shionogi & Co. Ltd., and UCB.