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REGULATORY

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Enrollment: More Than Numbers

Richard C. Walovitch, Vincent J. Girardi III, and John F. Tomera

Partnering with contract research organizations and using a blinded independent central review can help obtain a homogeneous patient population, increasing trial success.

PK in Late Phase Trials
Nitin Mehrotra, Yaning Wang, Venkatesh A. Bhattaram, Justin C. Earp, Jeffry Florian, Christine Garnett, Pravin R. Jadhav, Kevin Krudys, Joo-Hee Lee, Fang Li, Jiang Liu, Rajnikanth Madabushi, Anshu Marathe, Christoffer W. Tornoe, Hao Zhu, and Jogarao V. Gobburu

Collecting PK data in late phase trials led to alleviating additional trials, drug approval, and better dosing.
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There are a few significant questions to ponder as a result of recent or highly anticipated industry events. We look at potential changes to the outsourced clinical development industry by stratifying companies by size.

Small service providers can continue to stay the course and try to build their customer base through specialization (therapeutic, procedural, expertise) and relationship building, probably targeting small/emerging biotech companies. If you can find a sister company that can add capabilities/capacity without much overlap, then growing by merger is a real potential. The goal is to reach a critical mass large enough to play in the mid-size pharma segment.

Mid-size service providers are probably under some pressure, especially some of the larger ones that have been passed over in the recent merger activity. There are some obvious advantages to being a large, global, full-service service provider. This allows you to play in the sandbox with the large pharma customers, where clinical development activities are centralized. However, ISR’s research shows that sponsors are generally more satisfied with mid-size CROs.

Large service providers will start to feel more pressure from the new kids on the block; large pharma RFPs and awards will now be split among a larger group. How do you differentiate yourself once size is no longer the same strategic asset it once was?

Kevin Olson is CEO of Industry Standard Research.

Editor’s Note: The full text of this article is available in the Online Exclusives section.

Source Document Verification

In this analysis from Medidata Solutions, Insights Metric Warehouse, the company found a significant drop in 100% SDV in favor of a targeted sampling of subject eCRFs. This and clinical trials data from Tufts CSDD, TTC, ISR, and Medidata can be found at the Data Analysis section of our home page.

Source: Medidata Insights Metric Warehouse, December 2012

SDV coverage has shown a continuous decline since 2007.

Source: Medidata Insights Metric Warehouse, 2012-DEC

Refer to the Online Exclusives section for the full text of this article and other featured content.

Read on the Blog

Latest topic entries into the clinical trials blog site include biosimilars and generic reviews; patient-centered trials; missing clinical trial data; informed consent; and black box warnings. Read the blog at http://blog.appliedclinicaltrialsonline.com

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Early Lessons on Virtual Trials

Last month, Applied Clinical Trials spoke with Craig Lipset, Head, Clinical Innovation at Pfizer, about the current status of the REMOTE trial. Background articles on REMOTE and the participating vendors can be found in the August 2011 through November 2011 News sections.

What is the status of the REMOTE trial and what has been the general response to date to the virtual trial model?

There is different data that we’ll come out with over the course of the year sharing some of the status of the REMOTE trial in different settings. What I’ll say right now is that we’ve had great support from our technology partners. We’ve had great support from regulators and ethics committees. We’ve had some challenges in terms of getting significant numbers of patients into the study. And that’s okay because, in large part, if everything worked perfectly, then either we were geniuses or we didn’t push the boundaries hard enough.

While we may be smart, I think that we really wanted to make sure that we were pushing the boundaries here. And so we do view this as a learning project, where there are recruitment channels that we’re exploring that are not delivering. We’re capturing that data and reacting to it in real time and being able to make modifications in real time.

So there’s a great deal of learning that’s been happening over the recent few months around recruitment channels. In particular, where recruitment is entirely online and looking to see which ones are able to deliver this particular patient population, which is a unique population. These are patients that have to be very highly engaged, perhaps more so beyond that of a typical patient.

With your experiences to date, do you have any takeaways that you could provide for others looking to move toward a virtual model?

Make sure that the patients feel supported and that the process is as simple as possible.

By feeling supported, recognizing that in this model patients are not having that in-person physical engagement that they’re most comfortable with. And while many patients are comfortable doing a lot of transactions online, we have been educating consumers for years not to trust the Internet and not to trust sharing things over the Internet. And so we can’t just step right in and say, “Well, don’t trust anyone else, but you can trust us.”

So I think that we need to make sure that patients still feel a level of support. The intent with this model is not to say that there is no contact allowed with patients. The intent of the model is to make it more accessible and convenient. So phone conversations are completely fair to have. We have some experiments we’re doing with visiting healthcare providers to the patients. I think as long as we’re staying true to that goal of making the trial more accessible and convenient, we can do other things to make sure that the patient feels supported and well-engaged.

Around simplicity, clinical trials are complex. Informed consent forms are complex. And so everything that we can do to help mitigate that complexity, help make sure that things are both readily comprehensible but also that the workflow is simple, I think that those are important, early takeaways.

REMOTE Virtual Trial Stats and Facts

- REMOTE stands for Research on Electronic Monitoring of OAB Treatment Experience
- June 2011, Pfizer announces trial
- First-ever randomized clinical trial under an IND to assess the safety and efficacy using electronic tools
- Designed to test the methodology of the virtual trial concept, to determine if it can replicate the results of the previously completed Phase IV Detrol LA trial
- Detrol LA is a treatment for overactive bladder (OAB)
- Considered a patient-centered approach
- Technology partners: Mytrus, Exco InTouch, Greenphire, and Perceptive Informatics
- Clinicaltrials.gov identifier is NCT01302938
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FOR THE RIGHT QUESTION

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Research Fraud Requires Urgent Action

A new survey suggests that misconduct in research—or fraud—is not going away, and the issue still requires strong and concerted action from all parties.

The British Medical Journal (BMJ) received nearly 2,800 responses from clinicians and academics in the United Kingdom. Around 13% of the sample have witnessed colleagues intentionally altering or fabricating data during their research or for the purposes of publication, while 6% are aware of possible research misconduct at their institution that has not been properly investigated.

“While our survey can’t provide a true estimate of how much research misconduct there is in the United Kingdom, it does show that there is a substantial number of cases and that UK institutions are failing to investigate adequately, if at all,” noted Fiona Godlee, MD, BMJ Editor in Chief. “The BMJ has been told of junior academics being advised to keep concerns to themselves to protect their careers, being bullied into not publishing their findings, or having their contracts terminated when they spoke out.”

She added that the findings highlight the need for better systems to deter, detect, and investigate research misconduct. Some solutions are already being tested, and she hopes the survey will lead to action from the research community. “Doing nothing is not an option,” she said.

The full results were presented at a meeting held in London on January 12. It was hosted by the BMJ and the Committee on Publication Ethics (COPE), which aims for a consensus among institutions and funders towards tackling misconduct. In the survey, a total of 9,036 e-mails were delivered, and 2,782 (31%) responses were received. Of the respondents, 29% regarded themselves as clinicians, 42% as academics, and 29% as both.

“This survey chimes with our experience from COPE where we see many cases of institutions not cooperating with journals and failing to investigate research misconduct properly,” stated COPE Chair, Elizabeth Wager, PhD.

According to the authors, some National Health Service bodies blocked access to the survey website. Also, they admitted that some participants are not involved in research and have not had first-hand experience with it. Furthermore, research misconduct is a sensitive subject and they fear there may have been concerns over confidentiality.

On January 3, the BMJ also published a special issue about missing data in clinical research, arguing that this problem distorts the scientific record to the extent that clinical decisions cannot be based on the best evidence. Several comprehensive papers examine the extent, causes, and consequences of unpublished evidence, and they confirm that a large proportion of evidence from human trials is unreported, and much of what is reported is done so inadequately.

There is a “culture of haphazard publication and incomplete data disclosure,” according to an editorial by Richard Lehman, MD, from the University of Oxford, UK and Elizabeth Loder, MD, BMJ Clinical Epidemiology Editor. They call for more robust regulation and full access to raw trial data to allow better understanding of the benefits and harms of many kinds of treatment.

“When the word ‘mandatory’ turns out to mandate so little, the need for stronger mechanisms of enforcement becomes very clear,” they wrote, adding that concealment of data is a serious ethical breach and that clinical researchers who fail to disclose data should be subject to disciplinary action by professional organizations.

“The evidence we publish shows that the current situation is a disservice to research participants, patients, health systems, and the whole endeavour of clinical medicine.”

Other studies published in the special issue highlight the difficulties researchers face when they try to assess the true harms and benefits of common interventions. An article by Beth Hart, clinical research fellow and medical student at the Department of Clinical Pharmacy, Institute for Health Policy Studies, University of California, San Francisco, and colleagues, finds that including unpublished data in published meta-analyses of drug trials often changed their results. She argues that access to full trial data is needed to allow drugs to be independently assessed.

Further studies show poor adherence to requirements for compulsory trial registration and timely sharing of results. Joseph S. Ross, Assistant Professor of Medicine, Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT, and colleagues showed that fewer than half of US National Institutes of Health funded trials are published in a peer-reviewed journal within 30 months of completion. Andrew Prayle, NIHR doctoral research fellow, Queens Medical Centre, Nottingham, UK, and colleagues pointed out that only 22% of trials subject to mandatory reporting had results available within one year of completion.

A podcast on the issues raised by these studies is available at: http://www.bmj.com/multimedia.

— Philip Ward
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Virtual Training

PPD Trains CRAs in Three Dimensions

Clinical Research Associates (CRAs) at PPD receive standardized training so they can monitor trials the PPD way. Prior to June 2011, this geographically dispersed group of professionals would travel to the nearest PPD regional hub to undergo a 10-day course. In early 2010, Mike Wilkinson, Executive Vice President and Chief Information Officer of PPD, began looking for ways outside of traditional classroom training that would still produce the highest quality CRAs, but would also be more engaging to the CRAs, and maybe save travel costs in the end.

What Wilkinson found was a 3D virtual collaboration environment from ProtonMedia called ProtoSphere, which allows individuals to engage and learn in highly social, interactive, and visually appealing three-dimensional virtual spaces. ProtonMedia promoted its technology across industries for collaborative meetings and events, but Wilkinson saw promise for virtual training.

PPD’s clinical staff and its professional trainers spent three months adapting the company’s CRA training program, which had featured face-to-face training and PowerPoint, for the new virtual environment. The final product is now called PPD 3D.

3D Virtual Training

“It’s very immersive,” said Wilkinson of PPD 3D. “The CRAs create an avatar, which is a representation of you in the digital world. The CRA controls the avatar’s movement from room to room and certain gestures like raising a hand to ask a question. The CRAs are looking at the screen, but they are immersed in what their avatar is doing.”

For example, during one training session, the CRA goes with the trainer to the doctor’s office. In the traditional model, the instruction is given using PowerPoint, and then the trainer and a CRA would role play this interaction, with other classmates observing. With PPD 3D, the instruction takes place in the virtual world and each CRA enters a virtual doctor’s office, opens the virtual door, walks through and greets the avatar receptionist, sitting at the virtual reception desk. CRAs then engage in virtual source document verification.

Wilkinson explained that the CRAs don’t feel as if they are looking at a computer screen but like they are in the actual room. In addition, the program allows more customizations that are globally sensitive and appealing: avatars appear culturally appropriate and are actually greeted in the way of that culture.

“CRAs are required a day before to meet their tour guide in the virtual world for an hour so they understand what the process is and how to work in the environment,” said Wilkinson. “We’ve learned to make that tour guide culturally specific and aligned, and that makes the CRA much more comfortable.”

Wilkinson said another benefit of this technology is the cost savings. He said that PPD was able to realize return on the initial software investment within six months by eliminating travel to hubs for face-to-face training. They have completed 11 courses so far and now hold two virtual trainings per month, with plans to do as many as they can virtually. There is also the possibility of doing a hybrid approach—part virtual, part in person. Formal assessments of post-training test scores show that virtual training is every bit as good as traditional training. Based on engagement and feedback, there is a clear preference for the virtual training. Said Wilkinson, “They are having more fun and they are more engaged. They also send us suggestions on ways to improve the virtual training, and we have incorporated many of them.”

PPD is now working on initiatives to incorporate the technology for investigator meetings, team meetings, virtual visits to other offices, and more. For Wilkinson, the technology has brought together his former professional role with his present one. For three years, Wilkinson served as PPD’s Global Head of Clinical Operations, and prior to that he was the Global Head of Internal Medicine at another company. Eighteen months ago, PPD offered Wilkinson the opportunity to be CIO in an innovative capacity, integrating information technology, global training, business analytics, and process.
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Increasing the Use of Technology in Feasibility

For years ISR has tracked the dynamics that surround patient and investigator recruitment. Not surprisingly, the industry has challenges associated with recruiting patients into many of its clinical trials. These difficulties aren’t confined to just recruiting the patients. The industry has struggled—and continues to struggle—with predicting the recruitment of patients; the process known as feasibility in our industry. For years the industry has relied on poor quality databases, rudimentary questionnaires, and fading technologies to estimate trial recruitment. Even today 36% of the industry relies on fax-based questionnaires to prospective sites to generate recruitment estimates.

But there is reason to be hopeful. In 2009, as part of its Patient and Investigator Recruitment Success research, ISR asked industry representatives how often they rely on various information sources, processes, and technologies as part of their feasibility and trial planning process. Only 14% of respondents indicated they used electronic medical records data to estimate recruitment and 49% indicated an intention to increase this use. It turns out their predictions were correct. In its 2012 update of this research ISR found that 21% of respondents are using EMR data for feasibility estimates. And just as important, 52% indicate that their use of EMR will continue to increase over the next three years. —Industry Standard Research, www.ISRreports.com.

![E-mail-based questionnaires to sites: 64%](image)
![Fax-based questionnaires to sites: 36%](image)
![Third party benchmark data: 30%](image)
![Electronic medical records data (e.g., Cerner, Allscripts, McKesson, GE): 21%](image)
![Prescription data (e.g., IMS, VerispanSDI): 20%](image)
![Medical claims data (e.g., Blue Cross Blue Shield): 14%](image)

Source: ISR Reports

Participants were asked how often they rely on various information sources, processes, and technologies as part of their feasibility and trial planning process.
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Quality Approaches Key to Transforming Research

FDA wants sponsors to build quality into protocols, adopt risk-based strategies to streamline trials.

Empty drug pipelines and ever-rising clinical research costs are prompting extensive soul-searching for ways to make clinical trials more productive and better able to support drug discovery and development. Everyone agrees on the need for more relevant studies, more efficient research methods, broader public support for clinical trials, a stronger pool of investigators, and more rational regulation and oversight of research activities. There’s a healthy debate over how to get there.

Food and Drug Administration officials promote a shift towards a quality-based approach to protocol design and study management, along with revisions in specific policies to support risk assessment. Leaders of the US biomedical research community contemplate more “transformative strategies” that integrate clinical research into the nation’s healthcare system so it can tap electronic health records (EHRs). That would make it easier to identify patients suitable for clinical trials, record study data accurately and quickly, and document how new therapies can improve outcomes and reduce costs.

Evaluating risks

Adoption of quality-by-design (QbD) and quality risk management methods for clinical trial management is the current mantra at FDA. This strategy was discussed by agency officials and research executives at a workshop in August 2011 organized by the Clinical Trials Transformation Initiative (CTTI), a partnership between FDA and the Duke University Medical Center that has gained strong support from industry and the biomedical research community; future CTTI workshops will further explore the QbD approach to clinical research.

Anne Meeker-O’Connell, Associate Director of the Office of Scientific Investigations (OSI) in the Office of Compliance, Center for Drug Evaluation and Research (CDER), outlined the shortcomings of FDA’s current oversight model for clinical trials, noting that lax internal controls by study sponsors often lead to significant data problems and systemic errors in applications. Inefficient practices, she noted, consume valuable resources and undermine research quality. Ken Getz of the Tufts Center for the Study of Drug Development emphasized the need to adopt a quality approach, starting with protocol design to reduce study complexity and thus curb the need for multiple amendments as the study progresses.

The next step is for sponsors to develop an integrated quality management plan (IQMP) as part of protocol development. Under an OSI pilot, sponsors identify important risks and quality objectives to guide implementation of the clinical program. Metrics could include the number of subjects that fail to meet inclusion/exclusion criteria or a percentage of subjects with inadequate informed consent. Failure mode analysis can identify for sponsors what could go wrong and why, and how severely such problems would affect patient safety, data integrity, and protocol compliance. IQMPs may be particularly valuable for ensuring quality data from multi-regional clinical trials and for managing updates to research protocols in response to new information, problems with drug supplies, and unexpected events.

A recent FDA proposal for reducing excessive and costly clinical trial monitoring illustrates the tenor of the risk-based quality approach. Sponsors feel they have to verify all data at every clinical site to avoid regulatory problems, Meeker-O’Connell acknowledged, even though FDA permits a variety of monitoring approaches based on risks to human subject protection and data integrity of a trial. To promote change, FDA published draft guidance in August 2011 that encourages sponsors to design monitoring plans based on key risk factors: the complexity of study design and study population, investigator experience, data capture systems, and the relative safety of the investigational product. Sponsors should perform a risk assessment to identify what could go wrong with critical data processes, what would be the impact, and whether such problems could be detected readily, Meeker-O’Connell explained at the October 2011 FDA Inspections Summit sponsored by FDA News.

FDA also seeks to improve the quality and value of adverse event reporting from clinical trials, with an eye to reducing reports on less important, low-risk events in order to focus on more consequential safety issues. FDA issued revised regulations in September 2010 for safety reporting on experimental drugs, which clarifies responsibilities of investigators and sponsors for reporting serious, unexpected adverse events.
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adverse events. CTTI is further assessing thresholds for reporting serious AEs and ways to relate safety reports to underlying disease to help sponsors implement the new rules.

Internally, OSI is testing a risk-based model for planning its own clinical site inspections, initially for good clinical practice (GCP) inspections related to applications for new drugs and biologics; the plan is to extend this approach to oversight of institutional review boards (IRBs) and bioequivalence studies. This strategy also may be extended to OSI’s collaboration with the European Medicines Agency on parallel/joint GCP inspections. The regulators are sharing information on practices and schedules in order to improve methods, gain confidence in each other’s programs, and conduct more joint and parallel inspections to reduce redundant oversight.

**A quality approach to clinical trial management also should be part of a more comprehensive transformation of the US clinical trials enterprise.**

CDER Director Janet Woodcock noted that the demand for personalized therapies targeted to small patient populations illustrates the importance of integrating biomedical research into medical practice. Professional societies, payers, healthcare systems, and pharmaceutical companies all are important for establishing disease-based networks and supporting participation in and payment for clinical research; FDA, in turn, needs to expand concepts for assuring quality data from trials.

Amgen Senior Vice President Paul Eisenberg called for even more extensive reform of FDA’s “onerous IND process,” pointing out that the European Union’s simpler notification system doesn’t require a review of clinical trial materials and manufacturing processes at the research stage. US studies at multiple research institutions, he noted, are complicated by diverse contracting systems; variable informed consent and IRB procedures; and difficulties in managing privacy requirements. Central IRBs would help, as would harmonization of clinical trial applications, nomenclature, and electronic systems for reporting and assessing adverse events. Bryan Luce, Senior Vice President at United BioSource, urged “real regulatory reform” that permits earlier, conditional approval of new therapies based on evolving evidence, acceptance of new methods and “trust across regulators, manufacturers, and payers.”

**Broader change**

A quality approach to clinical trial management also should be part of a more comprehensive transformation of the US clinical trials enterprise, according to members of the Institute of Medicine Forum on Drug Discovery, Development and Translation. The forum has been weighing options for such change for several years and wound up its deliberations at a November 2011 workshop on “Envisioning a Future Clinical Trials Enterprise for 2020”—a final report is expected this spring.

The main conclusion of these experts is that clinical research needs to be linked more closely to the nation’s healthcare system in order to attract sufficient financial support to facilitate the development of new, important medicines. Despite years of discussion, the envisioned “learning healthcare system has not really come together,” commented Robert Califf of Duke University. Instead we have a process that “is slow, expensive, and often asks the wrong questions.” Protocols are complex and burdensome, he said; over 90% of trials don’t meet desired timelines, and many studies posted on clinicaltrials.gov are small and inconsistently utilize randomization, blinding, and data monitoring committees.

**Linking up**

Health system executives highlighted how health system data systems can provide an infrastructure to support clinical research. Richard Platt of the Harvard Pilgrim Health Care Institute and Harvard Medical School described the use of EHRs to identify and enroll children in a study on reducing obesity and to support a massive randomized study on how hospitals can identify strategies for reducing antibiotic resistant infections.

Another example is the Veterans Administration healthcare system, which has incorporated clinical studies into its healthcare program for years, according to Louis Fiore, head of the VA Cooperative Studies Program. Similarly, leading health plans around the country have joined the HMO Research Network, which now has some 20 sites at integrated healthcare systems that represent 10 million covered lives available for collaborative studies on vaccine safety, mental health, diabetes management, cancer, and other conditions. The aim is to conduct pragmatic, low-cost trials using EHRs to recruit, randomize, intervene and collect follow-up data, explained Karen Margolis of the HealthPartners Research Foundation. Centralized IRBs and template agreements on data sharing streamline operations, leading to strong patient retention, efficient adverse event surveillance, and ready dissemination of results.

The discussion ended optimistically as Douglas Cropper, CEO of Genesis Health System, a community-based health group in Iowa and Illinois with little involvement in clinical research, expressed a high interest in using EHRs to support trials and outcomes studies. He encouraged researchers to get health system CEOs and clinicians more involved by appealing to their business and clinical interests in improving best practices and better managing chronic disease, and by embracing quality improvement methods.
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Looking Beyond the Euro Turmoil

Europe’s struggling economies may have unexpected effects on the pharmaceutical sector.

The turbulence buffeting Europe’s economies is having multiple negative consequences—including in the pharmaceutical sector. Cash-strapped healthcare agencies are faced with ever-tighter public spending controls. Drug firms with significant presence in the eurozone are revising downwards their sales estimates and reconsidering their investment strategies. Uncertainty over the future is hitting long-term—and even shorter-term—planning in clinical development departments.

**Inner core**

Amid all the desperate macroeconomic remedies being canvassed, there are some that contain nuggets of thinking that could, over time, prove beneficial to pharmaceuticals in Europe.

The talk, in Brussels and beyond, is increasingly of a two-speed Europe—in other words, a rejigging of the 27-country European Union to create an inner core of more closely integrated countries with sound economies. Thus relegating less successful member states to an outer circle, a waiting room until they are ready to graduate to the elite class.

Just who would qualify for the inner core is still an open question, and need not detain us long here. Certainly it will not be the same as the 17-member eurozone—Greece, Portugal, Spain, and Italy would clearly not be eligible in the near future. Certainly it will not be just the prosperous countries, because consistently successful Sweden does not even use the EU’s single currency, and rich Norway is not even a member of the EU. Certainly it will not be just the big countries, because the UK is strongly opposed to the concept of closer links. But whatever its membership, the fuller integration it presupposes may contain the seeds of a solution to a dilemma that has made Europe a difficult arena for pharmaceuticals for half a century.

There is talk of a rejigging of the 27-country European Union to create an inner core of more closely integrated countries with sound economies.

An avant-garde of EU member states that pursue further and closer cooperation would have to decide how far that cooperation might go to ensure harmonious development. Already a new treaty is in the process of finalization among volunteer states that will bind them as never before on budgetary as well as monetary policy. There are other issues equally critical to closer economic alignment, such as taxation; labor market policy; and social policy, that have until now been jealously and ferociously guarded as the private preserve of individual member states.

**Health policy**

For the pharmaceutical sector, a shift towards alignment of health policy—also until now a matter reserved purely for autonomous national decision-making—could, if it occurred, mark the start of a revolution. It could mean the end of that still-unbridged gulf between the European and national dimensions of medicines policy that has bedeviled drug supply and development in Europe. No longer would distinct national pricing and reimbursement systems complicate product launch. No longer would national regulatory agencies insist on treating the same product in different ways. And no longer would multinational clinical trials have to fight their way through a jungle of conflicting national views.

**Straws in the wind**

While we are in the straws in the wind department (although on a less cosmic level), it is worth noting in
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passing that two major—but hitherto proudly separate—European industry associations in the healthcare area have just decided to join forces. EDMa, the European Diagnostic Manufacturers Association, and Eucomed, the European medical technology industry association, say their declared aim is to “ensure the place of in-vitro diagnostics and more wide ranging mergers between industry associations occur? 
Back in the more immediate world of current affairs in strictly pharmaceutical affairs, it is impossible to ignore the fact that Europe is in a heightened state of expectation over the impending release of the proposal for an update of the clinical trials directive, which is still not out as of presstime.

One of the chief preoccupations of the European Medicines Agency for 2012 will be implementing the EU’s new pharmacovigilance legislation.

Tightening pharmacovigilance
One of the chief preoccupations of the European Medicines Agency for 2012 will be implementing the EU’s new pharmacovigilance legislation and balancing its introduction with budgetary and other resource constraints. From July 2012 it will start putting the plan into action. The new Pharmacovigilance Risk Assessment Committee will have its inaugural meeting in July, and the revised Coordination Group will start operating in September, at the same time that the agency begins to use the new urgent procedure and public hearings.

It won’t be simple. The agency will give priority to the elements in the legislation that contribute to public health. The next priority will be activities increasing transparency and improving communication. Only after that, if resources allow, will attention be given to simplification measures.

As if that wasn’t complex enough, the European Union is also aiming to introduce yet more pharmacovigilance legislation this year. The proposal, which tightens up drug monitoring rules, and, notably, prevents companies from discreetly withdrawing products without any clear explanation, was the sole focus of the EU Council’s working group on pharmaceuticals, which met in Brussels in mid-January. The new elements are designed to plug the loopholes that were revealed as the Mediator safety case unfurled in France.

Early last year, EU officials initiated stress-tests to see how far their newly-adopted drug-monitoring rules were capable of preventing another similar case. The tests showed gaps, which is why these additional proposals were quickly put together. In addition to requiring companies to explain any product withdrawal, these planned changes will provide for an automatic pharmacovigilance procedure. This will apply even to products that have not been authorized through the European Medicines Agency’s centralized procedure.

The automatic check is intended to come into effect “in the cases of specific serious safety issues with nationally authorized products, with a view to ensuring that the matter is assessed and addressed in all member states where the medicinal product is authorized.”

Electronic health records
Look for an increasing shift towards electronic data use. A European survey claims wide support for using electronic health records for clinical research. One of the projects supported by the Innovative Medicines Initiative checked out opinions among researchers in academia; the pharmaceutical industry; system providers; and patients’ organizations, and it reports that more than nine out of 10 respondents favor this approach. The goal of the project is to come up with a platform and business model to enable the re-use of data from such records for clinical research in Europe. Most of the responders to the survey highlighted the need to ensure that using electronic records is not going to fall foul of legislative, regulatory, ethical, and privacy requirements. But the impartiality of the results may be influenced by the nature of the project, whose title is a clear indication of its intention: Electronic Health Records for Clinical Trials.
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Big Data, Information and Meaning

Vendors have developed systems for massive databases, but are we data ready?

I often wonder how people with jobs like me find time to read books anymore. By the time I’ve gotten through a day of meetings, e-mail, and business reading, there’s not much time to absorb anything else other than a newspaper or a favorite periodical. My solution has been to listen to audiobooks during my daily morning workouts. I usually confine myself to non-fiction business, science, and history books to help maintain a semblance of self-improvement, even though listening to a book does not quite achieve the same level of understanding as reading by eye.

Once in a while, I pick up a book that is so compelling or complex that I find myself having to go back and purchase a print edition afterwards so I can read it the traditional way. This past holiday, such a book was “The Information: a History, a Theory, a Flood” by James Gleick. Gleick captivated me as he traced the history of communication, writing, messaging, cryptography and, ultimately, computing from ancient times through pioneers like Charles Babbage, Claude Shannon, and Alan Turing. It was surprising to me that the term “information” did not really exist prior to the middle of the 20th century—when people probably had the time to not only read real books, but also write letters and converse in leisure—and how critical information theory was in leading the way to computers, the Internet, and today’s wireless computing world.

As Gleick portrayed the transition from the spoken to written word, and from paper to bits, I found myself wondering how we’re progressing as we handle information in the world of clinical research and development.

One new trend to consider in this light is “big data,” which refers to databases, measured in terabytes and above, that are too large and complex to be used effectively on conventional systems. Big data has attracted big vendors who have developed powerful new systems that combine massively parallel hardware and software to quickly process and retrieve information from such immense databases. In our world, big data solutions have been mostly employed to date in bench-research applications. In such cases, scientists have already gained experience in how to represent molecular, genomic, proteomic, and other complex, voluminous data types well enough so that they can benefit directly from the speed of processing and retrieval of big data appliances.

Projects like OMOP, Sentinel, and EU-ADR are raising interest in exploring healthcare data, and available data sources and tools are improving all the time. For example, the UK government has recently announced its intention to make available National Health Service data to the R&D community. Yet while projects like OMOP reflect cross-industry, cooperative efforts to better understand methods and develop open source tools, sponsors are still locked into creating their own local copy of a research database by contracting with individual data providers one at a time and building their own data repository.

It would be much more logical and efficient if the industry could work together to make such data of common interest available to all—as a public research “big data commons in the cloud,” which would eliminate the need for everyone to set up their own local environment populated by the same

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Big data refers to databases, measured in terabytes and above, that are too large and complex to be used effectively on conventional systems.

But it seems that such systems would also be very useful for examining large observational healthcare databases of millions of patients to try to identify and explore safety signals. Yet it is extremely challenging to meaningfully merge and combine such data into a single research database, because the content, context, and structure of such data from different sources is so heterogeneous. Continual movement toward electronic healthcare records, together with advancements in standards and systems may get us closer eventually, but the path will likely continue to be long and tortuous. And the current business model of either tapping into a data provider’s system one at a time, or downloading local copies of each data source, coupled with the risks of maintaining privacy and compliance compounds the problem.
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external data sources over and over again. Of course it would certainly be challenging to establish an effective cooperative legal/business model and infrastructure to serve the interests of many different stakeholders, including pharmaceutical manufacturers, researchers, regulators, and even health-care providers and payers.

**It would be more logical to make data available to all—as a public research “big data commons in the cloud.”**

As daunting as this seems, it’s even more of a stretch to create such a big data commons for non-clinical and clinical study data resources from products in development, which have traditionally been treated as highly proprietary intellectual property assets that sponsors guard closely. In this case the pooling of data is confounded not only by the lack of standardization in data structures and terminologies, but also by the need to understand differences in study context which is recorded in the clinical study protocol, still typically an unstructured text document. So it’s difficult to justify a big data scenario because such data are not readily available (although FDA, continues to try to build its own clinical trials repository in the latest iteration of the Janus program), as well as so hard to pool together. CDISC has helped here by providing standard representations for many commonly used data domains, but these standards did not originally extend to the specific data elements and efficacy outcomes associated with each individual therapeutic area.

This too is changing, as has been demonstrated by the Critical Path Institute, which has put together a research study database of Alzheimer’s treatments in CDISC format contributed by many different sponsors. This model of using core CDISC metadata standards extended to incorporate data elements specific to a disease to define a single way to represent data for studies in a specific therapeutic area, together with providing a database of actual study data available to the research community is now being extended to many more diseases. CPath thus offers a prototype of a commons, though hardly a big data scenario yet.

Defined metadata standards for such projects describe the concepts, elements, terminologies, and relationships between them for research in a specific therapeutic area. In a sense, a structured protocol consists of metadata about a trial, some of which may be recorded in a registry like clinicaltrials.gov. Such information, and the more complex aspects of a protocol such as the treatment plan and the procedural and data collection times and events must also be captured and bound to the actual data so that researchers can understand the nuances of each trial that might affect the understanding of the data pulled from a big data repository.

The concept of metadata can be extended to address data provenance as well. In clinical research, provenance involves the ability to trace the differing states and chain of custody as data moves from patient through investigator, CRO, sponsor, and regulator—from origin through analysis. The NIH-sponsored National Children’s Study (NCS), a large-scale, prospective observational study to examine factors that can affect the health of our nation’s children as they develop into adulthood, is taking a particularly ambitious and innovative approach to recording provenance. This project recognizes that scientific concepts and data standards will evolve over time, so its ambitious metadata repository seeks not just to describe the metadata about study elements, but also metadata to describe the transformation of concepts and research practices over time. It will be interesting to see how this project itself learns and evolves over its expected lifecycle of more than two decades, and will probably want to accommodate many innovative changes in technology during that lifespan.

Now, much of the information NCS (or any clinical trial) needs is the same information that would be logically present in observational data sources, and wouldn’t it be exciting if our hypothetical data commons for observational healthcare data could be utilized side by side with our standardized repository of non-clinical and clinical trials as well. To do this we need common semantics, and common ways of modeling patient data between these two worlds. This reverie is unlikely to be achieved by any single system of global standards, so it must find a way to equate various clinical models and map terminologies to at least enable the possibility of interoperability. One great hope to achieve this vision is the Clinical Information Modeling Initiative (CIMI), a global cooperative effort being led by Stan Huff, MD, of Intermountain Healthcare. CIMI is working to define a common reference model and base set of terminologies for representing health information content that will enable health information to flow from one standard representation to another both within the world of healthcare and onward to clinical research.

We need big data, big metadata, and big ideas. To achieve this we need to bring together all available data in a way that expresses a common meaning, irrespective of its original form. Because in the end, knowledge comes from consistent information, and, as Gleick recognizes, it should not matter whether it is spoken, or written, or transmitted in many different forms—the meaning of the message must be one if we are to effectively learn from it. ❑
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When it comes to gaining regulatory approval in a clinical trial, controlling variability is essential, especially in pivotal Phase III trials. It is here that the patient population being studied can not only end up determining the potential market size for a drug, but also impacts the drug’s efficacy conclusion to determine if it meets its primary endpoint. Performing an independent analysis of the data, such as a patient’s diagnostic status, can have a significant impact on minimizing variability and is hence why patient enrollment plays such a key role in determining a trial’s outcome.

Identifying the upfront problem

Too often patient enrollment is recognized as a numbers game where the objective of meeting aggressive enrollment rates is mistakenly achieved by enrolling patients who may not always meet all the inclusion or exclusion criteria. This is a common systemic issue that may be due in part to sites trying to meet aggressive enrollment goals or clinical operations staff trying to meet corporate mandates. This is usually done one of two ways, either the investigator enrolls a patient who they admit does not meet the inclusion/exclusion criteria and asks for a protocol exemption/waiver, or their view of the subjective patient enrollment data is biased by the interest to push the enrollment rate up. The first is easily tractable since detailed records of the exemption granted by the sponsor are monitored whereas the latter is more problematic, insidious, and requires active detailed monitoring and in many cases would benefit greatly by a blinded independent central review (BICR). Regardless of the cause the result is the same: a decrease in homogeneity of the population. This problem only seems to be growing and, although it is tracked in most Phase III trials by looking at the size of the intent to treat (ITT) population as compared to the per protocol population (PPP), it remains an area of minimal focus.

Since most registration trials require that the ITT population be used in the primary analysis, drugs are being evaluated with up to 50% of patients comprising the per protocol population (i.e., total pooled ITT population of 937 patients, of which 493 comprised the per protocol population). This added heterogeneity usually means an increase in variability of response and can put meeting the trial endpoints at risk. In addition, the potential for GCP violations due to multiple enrollment exemptions can often cause serious regulatory compliance issues.

Pre-enrollment BICR of subjective enrollment criteria can play a significant role in controlling...
study population heterogeneity and has the potential to improve trial outcome. Using a BICR to evaluate patient inclusion/exclusion criteria can bring better standardization to the patients enrolled and mitigate variability. BICR are advocated by the FDA and are commonly performed in oncology registration trials when the trial’s primary endpoint is based on tumor imaging. BICRs are usually done by contract research organizations (CROs) who manage the process and describe the procedures as it relates to acquiring the data, training the independent reviewers (IR), and monitoring the IR performance during the conduct of the study.

In most trials there are two opportunities for a BICR to provide objective review of potential trial patients. First is the inclusion/exclusion criteria assessment and then again upon enrollment, but before randomization, when multiple screening tests are performed. These assessments can be either a simple review of subjective criteria (e.g., cardiac echo quality) or a complex review requiring multiple clinical experts and multiple imaging studies (e.g., early Alzheimer’s).

The inclusion/exclusion criteria should be based on both the sponsor’s knowledge of the action or effect of the investigational material and on information from prior studies. Exclusion criteria should not be so restrictive that the available population is too limited to obtain the enrollment goal. However, the inclusion criteria should not be so lax that the acceptable population becomes too broad to prove effectiveness of the study article. Once it has been determined that the patient has met the inclusion/exclusion criterion, the patient is enrolled in the study. After enrollment, but prior to receiving on-study treatment, subjects are screened to establish a baseline for their conditions to determine the degree of disease burden so that the patient may be stratified for randomization.

Imaging studies and pathological assessments are often important subjective assessment parameters that play a role in all parts of a clinical trial (enrollment, on study assessment, and patient outcome). This is most evident in imaging studies where the FDA has commented on the

**Inclusion/exclusion criteria should be based on the sponsor’s knowledge of the action and on information from prior studies.**

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variability of on-site radiological assessment and the need to control variability. Unfortunately, many companies are often in a rush to enroll/randomize patients and thus depend on on-site assessment of disease burden and/or disease staging. This can create problems particularly when the subjective assessment is difficult to determine and requires a great degree of precision.

Precision is obtained by making multiple independent assessments of a parameter. These assessments are regularly performed by a BICR following a multi-read adjudication process, which is seldom done in a clinical setting. This can be a major issue in open labeled trials, which require a BICR to determine on-study response to treatment. A recent example of this is a hepatocellular carcinoma (HCC) trial in which the site enrolled a patient based on the results of a site read of a liver CT but the CRO sub-specialty radiologists repeatedly indicated that the lesion was just a hemangioma. In this case, the patient baseline status can’t change and since the patient doesn’t have HCC, he/she is assured not to be a responder. One way of handling this issue is to reclassify the patient. This is often done by changing patient status from PPP to ITT populations (see description below). This issue can often be avoided when independent experts are used for both screening and on study reads.

**PPP and ITT populations**

When the analysis is restricted to the participants who fulfill the protocol in terms of the eligibility, interventions, and outcome assessment, the analysis is known as an “on-treatment”, “on-study,” or “per protocol” analysis. The per-protocol analysis restricts the comparison of the treatments to the ideal patients; that is, those who adhered perfectly to the clinical trial instructions as stipulated in the protocol. This population is classically called the per-protocol population and the analysis is called the per-protocol-analysis.

In the ITT population, none of the patients are excluded and the patients are analyzed according to the randomization scheme. Medical investigators have often expressed difficulties in accepting the ITT analysis, even though it is the pivotal analysis for the FDA and EMA. This analysis is generally favored because it avoids the bias associated with the non-random loss of the participants. Nevertheless, the ITT analysis by definition includes patients who don’t meet the inclusion and exclusion criteria and may not have the disease the sponsor is targeting (as was the case in the hemangioma example in the HCC trial discussed above). This can have a significant impact on a drug’s chance for success. To demonstrate this issue, the following provides an example of how ITT, which is >15% larger than a PPP, can result in a drug not hitting its primary endpoint.

Assume an open labeled oncology trial where participants are equally randomized into an active control arm and an investigational drug arm. There is an aggressive push for enrollment from the sponsor, and the investigator thinks the test treatment has a much better chance of treating the patient than the control arm treatment. Therefore, he/she decides to enroll more “borderline” eligible participants to the treatment arm than the control arm with the intent of using the new drug to help a wider range of patients.
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Latter evaluations are performed by personnel with variable medical imaging experience who have not gone through detailed training.

The primary endpoint of the trial is to determine if the investigative drug shows superiority for progression free survival (PFS). Based on previous studies, it is estimated that the response rates for the treatment and control arms are 0.5 and 0.4 respectively. As such, 390 participants are enrolled in each study arm in order to obtain 80% statistical power for the primary endpoint analysis.

Assume that a certain percentage of the participants were retrospectively found to be either tumor-free or non-responsive to treatments because the patients did not have target disease and a slightly higher percentage of these deviations were found in the treatment arm due to investigator bias (i.e., 60% vs. 40% for control). These participants will therefore not be able to show full response; however they will still be included as part of the ITT analysis. PFS rates in both arms will drop, making it more difficult to show superiority and diluting the treatment effect.

We are testing the hypothesis that the test arm is superior to the control arm, with an alpha of 0.05. We assume that the response rates for the eligible patients in each arm will be consistent with past studies. Figure 1 demonstrates how the eligibility status of our patient population can effect the ability of a trial to show a significant treatment effect. The horizontal line represents the 0.05 alpha level, p-values to the right of the line are not statistically significant. If 15% of the participants are found not to be tumor-free upon enrollment, the expected significance of the treatment effect is borderline at the 0.05 level (p-value=0.048). If the percentage rises to >15%, the effect is not significant.

Subspecialty assessment
Differences between institutional assessment (i.e., on-site reads) and BICR have been observed in studies and have been a topic of recent debate, particularly as it relates to on study progression of disease as determined using radiological assessments. The focus of this debate is centered on informativeness of a process that does not apply to enrollment assessment.

Although much attention has been paid to the need to standardize the performance and acquisition of imaging in oncology trials, the on-site image evaluation process remains much less controlled. Usually, these latter evaluations are performed by personnel with variable medical imaging experience who have not gone through detailed training and whose performance is not tested regularly. Typically, there is a pool of readers attached to each site and up to a few hundred readers in total who make measurements and complete case report forms. All too frequently, radiologists are not co-investigators and have not signed the FDA Form 1572, so there is minimal imaging oversight and review on performing the image acquisitions. Additionally, there is often no dedicated training for performing the image evaluations that conform to the requirements of a well-controlled multi-center trial (e.g., Response Evaluation Criteria in Solid Tumors, Cheson, etc.). While the standard of care for clinical interpretation of images by a radiologist at a site may be sufficient for patient management, a radiologist’s clinical report is generally insufficient for selecting and measuring lesions required in a clinical trial.

In contrast, in independent blinded evaluations, images on which efficacy is based are almost always read by radiologists who are trained in the related specific indication. Prior to the readers beginning evaluation of the images, they are trained and tested in a standardized, validated and documented fashion. These central reviews are conducted by a small number of reviewers with specific expertise, thus lessening measurement variability. Also, prospective trial-specific training and testing of readers further reduce measurement variability. Most importantly, the central review complies with the regulatory training requirement to “train the qualified readers prospectively.” More than 15 years ago, it was recognized by industry, FDA, and other regulatory bodies that if image evaluations were to be used as a measure of efficacy, a controlled evaluation process was required. Not much has changed in the quality of site reads since that time.

The problem with trying to understand the added value of independent assessment is complicated by the difference between degrees of independence (i.e., lack of complete independence of the site assessment compared to the complete blinded assessment performed by an independent core laboratory). The integrity of the blinding to treatment process can sometimes decrease accuracy of assessment and this trade-off must be compared to the importance of obtaining the data without bias. Since the objective of pivotal trials is to perform a study for regulatory approval the goal of the study is not the practice of clinical medicine but more in the domain of regulatory science in which removal of bias is an important component. This concept does not resonate with everyone, particularly healthcare providers, but the effects of bias can have a major impact on results. For example, when comparing site readers to an independent blinded read in a dementia trial using SPECT perfusion imaging, the data was similar and the variability between site reads and independent reads were fairly uniform across centers with one noted exception: a site reader who had almost a perfect positive predictive value
for diagnosing Alzheimer’s disease. After investigation, it was determined that >90% of his patients came from a longitudinal Alzheimer study being conducted at the hospital. This example demonstrates how controlling for bias can have a profound effect on reader performance, thus necessitating the need to measure variability. The statistical measurements of variability between readers (inter-reader variability) and within readers (intra-reader variability) is something that is often not well understood and seldom done when assessments are performed in clinical practice or when on-site assessments are used in clinical trials. This is unfortunate and can be a problem because sites are trained at the beginning of a trial; that is when terms are defined and criteria are set for making an assessment. It is well known that if those criteria differ from criteria used in clinical practice, a process called definitional drift can occur over time.

Two examples which emphasize the need to focus on subspecialty trained experts to preclude issues that could involve misinterpretation of subjective data include the following:

- **Hemangioma vs. hematoma.** From a white paper concerning the European Congress of Radiology 2010 in Vienna, it was reported that Gerd Schueller, MD, a radiologist at the Medical University of Vienna stated that for oncologic imaging, and for that matter emergency imaging, hemangioma of the liver does not look like a hematoma of the liver, and that “we have to learn the differences.” The need for subspecialty expertise is real and cannot be ignored.

- **Breast cancer diagnosis variability.** A disfiguring lumpctomy has occurred only for the patient to learn that there was no cancer present. Even though rare, this is not an entirely uncommon event. Such events can occur when the variability of either pathological or radiological assessments are not controlled. Implications of uncontrolled variability per pathological15, 16, 17 and radiological1, 18, 19, 20, 21, 22, 23 assessments collectively compound maximum diagnostic performance to poor prognostic ability. To put it another way, when the false positive rate is 10% for both radiological and pathological assessments, maximum diagnostic performance can only be approximately 81%. Consequently, the inherent lack of control of variability within each subspecialty discipline (i.e., radiology and pathology) lessens the integrity of the diagnosis as well as the prognosis. A pathologic diagnosis is the foundation upon which all other treatment decisions are made and with breast cancer, the pathology dictates the use of potentially curable therapy. Incorrect pathologic diagnoses may lead to negative outcomes as serious as failure to treat a missed case of breast cancer or provision of unnecessary surgery, chemotherapy, and radiation. In 2010 a review10 of 2,564 cases from the Sloane Project reported that in 30% of patients undergoing breast-conserving-surgery for ductal carcinoma in situ, preoperative imaging underestimated the extent of disease resulting in a requirement for further surgery.

**What role does the CRO play?**

It’s not necessary for all subjective assessments to undergo a BICR process, but assessments that are both difficult to make because they require extensive experience and those that are part of important endpoints of the trial can realize tremendous value from working with a CRO whose expert independent reviewers are subjected to a rigorous training and variability testing. These factors combined with a multi-read adjudication process will maximize the potential for obtaining unbiased accurate data with maximal precision. Since Phase III trials are large (in some cases 100 sites and lasting several years), it would be a logistical nightmare to have to perform intra- and inter-reader variability testing with 100 local reviewers that may require retraining throughout the course of the trial. The BICR read team is much smaller and thus facilitates the ability to determine variability and to retrain as a team or individually if needed.

Identifying what subjective assessments are important to have independently reviewed is not always straightforward, although it is often clear what assessment(s) will have an impact on trial outcome. The variability of making that assessment is not often well understood. Understanding variability requires statistically accounting for chance agreement. This is where experienced CROs that have done these diagnostic assessments can provide value. CROs provide the experience necessary to collect variability data and understand the reproducibility of the measurement since they regularly deal with a limited pool of independent reviewers (i.e., radiologists and pathologists) and have criteria for testing and retraining. If needed, they can determine if definitional drift occurs by performing intra-reader variability testing.

CROs also possess the knowledge and experience in both determining if the subjective assessment needs to be independently reviewed and the understanding of what type of training and retesting of independent reviewers needs to be performed during the trial so that precision and accuracy are maintained. However, since the eligibility criteria often requires experts from multiple disciplines who have experience in diagnosing uncommon diseases, the CRO has to have the ability to leverage the subspecialty experts who are needed to make the independent assessments. This requires both strategic relationships with leading academic and tertiary care institutions and advanced digital portals.
...so that a review of images and other data can be done at remote locations.

**Conclusion**

An experienced CRO can play an important role in strictly enforcing per-protocol criteria determining what patients get into the trial. Through their enforcement of strict criteria for inclusion and exclusion, as well as through their ability to manage and facilitate a relationship involving subspecialty screening, CROs can positively impact trial outcomes to be more robust, homogeneous, and aligned to regulatory compliance with all bias minimized.

**References**


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*To whom all correspondence should be addressed.*
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PK in Late Phase Trials

Collecting PK data in late phase trials led to alleviating additional trials, drug approval, and better dosing.

Pharmacokinetic (PK) data (plasma drug concentrations) are routinely collected in early clinical studies. Several regulatory guidances describe the role of PK data in regulatory decisions. From an industry perspective, delineating PK characteristics in early phase clinical trials aids in the selection of the promising molecules and helps to make a go/no-go decision. However, the value of collecting the PK data, which typically entails sparse blood sampling (few samples collected per patient), in late phase clinical trials is not well appreciated or documented. In spite of regulatory guidances (population PK, exposure-response, dose-response) recommending collection of PK information in late phase (Phase II-III) clinical trials, whether to collect PK data in late phase clinical trials is still routinely debated. Industry scientists often are asked to justify the value of collecting PK information in late phase clinical trials. Practicality and costs are often presented as challenges that limit collection of PK.

There is no systematic documentation of the value of collecting PK data in late phase clinical trials either from a drug development or a regulatory perspective. Late phase clinical trials are mainly composed of early patient, dose-finding, pivotal, or registration trials. In the context of this article, both pivotal or registration trials, and those trials that have similar endpoints as the pivotal trials, such as Phase II dose-ranging trials, are considered late phase clinical trials.

The objective of this article is to systematically evaluate the role of PK collected in late phase trials in key regulatory decisions such as drug approval and labeling.

Materials and methods
Overall we utilized three approaches to evaluate the value of collecting PK in late phase clinical trials: internal experience, external survey, and selected case studies.

Internal experience. We documented the final regulatory action for each of the new drug applications (NDA) and biologic license applications (BLA) submitted between 2002 and 2008 which required pharmacometrics review. Almost all submissions for a pediatric indication include sparse PK sampling in late phase trials, which critically drive the dosing decisions. Hence, pediatric submissions were excluded in the current survey. The survey included submissions for new molecular entities or new indication claims. Specifically, the following information was noted: availability of PK data with respect to the amount (number or percent of patients contributing to PK information) and type (rich/sparse/mix), role of PK in approval related decisions (pivotal/supportive), role of PK in labeling decisions (pivotal/supportive), and the role of PK in alleviating the need of additional trials (yes/no).

Population PK and exposure-response modeling were the predominant pharmacometric approaches used. Approval related decisions imply approval, approvable, not approvable, or complete response. Prior to August 11, 2008, approval related decisions by FDA’s Center for Drug Evaluation and Research were categorized as “approval,” “approvable,” or “not approvable.” Since then, instead of an “approvable” or “not approvable” letter, a “complete response” letter is issued to the applicant stating that the review
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Questions Included in External Survey

<table>
<thead>
<tr>
<th>Question (A)</th>
<th>Question (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons in Favor of Collecting PK Data</td>
<td>Reasons Against Collecting PK Data</td>
</tr>
<tr>
<td>1 Used as evidence to support the proposed dosing regimen</td>
<td>Cost</td>
</tr>
<tr>
<td>2 Conduct exposure-efficacy analysis (e.g., to demonstrate evidence of effectiveness)</td>
<td>Practicality or feasibility</td>
</tr>
<tr>
<td>3 Conduct exposure-safety analysis (e.g., to justify dose modifications)</td>
<td>Sufficient PK information from earlier trials</td>
</tr>
<tr>
<td>4 Evaluate the effect of extrinsic (drug-drug interactions, etc.) and intrinsic (age, hepatic impairment, etc.) factors to support proposed dosing regimen</td>
<td>Other</td>
</tr>
<tr>
<td>5 Other</td>
<td></td>
</tr>
</tbody>
</table>

Source: Nitin Mehrotra et al.

Table 1. Questions included in the external survey for reasons in favor of collecting PK (A) and against collecting PK (B).

External Survey Responses

<table>
<thead>
<tr>
<th>In Favor of Collecting PK Data</th>
<th>Percentage of People Ranking Most Important (Rank=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support dosing recommendations</td>
<td>28</td>
</tr>
<tr>
<td>Exposure-efficacy (e.g., evidence of effectiveness)</td>
<td>41</td>
</tr>
<tr>
<td>Exposure-safety (e.g., justify dose modifications)</td>
<td>35</td>
</tr>
<tr>
<td>Evaluate effect of intrinsic and extrinsic factors</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Against Collecting PK data</th>
<th>Percentage of People Ranking Most Important (Rank=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>20</td>
</tr>
<tr>
<td>Practicality or feasibility</td>
<td>51</td>
</tr>
<tr>
<td>Sufficient PK information from earlier trials</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: Nitin Mehrotra et al.

Table 2. Summary of responses obtained via external survey highlighting the reasons in favor or against collecting PK data in late phase clinical trials.

period for the application is complete and it cannot be approved in its present form. The complete response letter describes specific deficiencies and when possible provides recommendations that the applicant might take to get the application ready for approval. The question on labeling was only applicable if the NDA or BLA was approved. The ranking choices included “pivotal,” “supportive,” “none,” and “not applicable.” If the availability of PK was critical in the regulatory decision, it was ranked “pivotal.” That is, without the analysis involving PK information the regulatory decision would have been different. On the other hand, if the PK information was worthwhile in confirming the regulatory decision, it was ranked as “supportive.” It should be noted that often supportive evidence is also required by the FDA to make decisions related to approval and labeling. Sparse PK information implies that few samples are collected from each patient in the trial, while rich PK information implies that complete concentration-time profiles were determined. The choice “mix” implies that some patients contributed towards rich, while some contributed towards sparse PK sampling.

External survey. An external survey was conducted in order to gain insights into the importance of PK data collection mainly from the pharmaceutical industry perspective. Clinical pharmacology scientists at pharmaceutical industries, academia, and contract research organizations (CROs) were asked to rank their choices on the following two questions as described in Table 1. The survey was posted on the Internet via two clinical pharmacology related online user forums (PharmPK and NMusers).

Pharmaceutical scientists were asked to rank each of the five responses under (A) and four under (B) from least important (rank=1) to most important (rank=5). The results are tabulated as percent of responders selecting the highest rank to each of the choices for questions A and B.

Case studies. Case studies were selected that illustrated the role of collecting PK in late phase clinical trials. In general, the impact of PK collection is presented for the following areas:

Results

Internal experience. There were 79 applications (66 NDAs and 13 BLAs) submitted between 2002 and 2008 that required pharmaceutics review. Of the 79 applications, 62 involved new molecular entities while 17 involved drugs that are already approved but were submitted to the FDA
to seek a new indication. The impact of the PK information collected in late phase clinical trials on approval and labeling decisions is presented in Figure 1. Of the 79 submissions, 70 had PK data collected in the late phase clinical trials. A majority of the applications involved collection of sparse PK (61%), 35% had a combination of sparse and rich PK sampling, and approximately 4% involved rich PK sampling, in the late phase trials. Of the 39 reviews that had an impact on approval related decisions, 11 (28%) alleviated the need for additional trials. Of the 41 reviews in which PK was pivotal or supportive in labeling decisions, 13 (32%) contributed to statements in the dosage and administration section; 12 (29%) to the specific population; 4 (10%) to contraindications, warning, and precautions; and 34 (83%) to the clinical

Source: Nitin Mehrotra et al.

Figure 1. The impact of PK information collected in late phase clinical trials in approval and labeling decisions.
Exposure Comparison

<table>
<thead>
<tr>
<th>Observation from Phase III</th>
<th>Adjusted AUC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{24}$ (ng*hr/mL) range</td>
<td>Data N= 577</td>
</tr>
<tr>
<td>Percentage of subjects with AUC &gt; 70,000</td>
<td>0%</td>
</tr>
<tr>
<td>Percentage of subjects with AUC between 50,000 to 70,000</td>
<td>0.35%</td>
</tr>
<tr>
<td>Percentage of subjects with AUC between 30,000 to 50,000</td>
<td>0.69%</td>
</tr>
<tr>
<td>Percentage of subjects with AUC between 10,000 to 30,000</td>
<td>16.81%</td>
</tr>
</tbody>
</table>

*Each AUC was multiplied by 1.85, to account for administration of lopinavir/ritonavir rather than darunavir/ritonavir, assuming an 1.85 fold increase in exposure. The percentage of subjects who will actually receive drugs that increase etravirine exposure needs to be accounted.

Source: Nitin Mehrotra et al.

Table 3. Comparison of expected etravirine exposure in a population that might receive etravirine (200 mg bid) with lopinavir/ritonavir and exposure observed in registration trials.

The analysis was focused on the patients in the highest exposure quartile of the registration trials with two specific aims:

- To derive the expected distribution of etravirine concentration across a population that might receive etravirine in combination with lopinavir/ritonavir, and compare it to exposures observed in the registration trials.
- To compare the adverse event profiles in the highest exposure quartile (AUC 6500-64000 ng*h/mL) to the patients in the lower three quartiles. Safety analyses consisted of comparison of common adverse events and evaluation of select laboratory abnormalities.

Pharmacokinetic data were available for 96% (576/599) of the etravirine treated patients. The expected distribution of etravirine concentration was achieved by multiplying the highest etravirine AUC value observed for each subject with pharmacokinetic data in Phase III by a factor of 1.85.

Table 3 illustrates a comparison of observed and expected etravirine exposure by different AUC cut-offs. In the observed data, AUC greater than 30,000 was observed in <2% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. However, ~6% of patients were expected to have AUC greater than 30,000 if etravirine is administered with lopinavir/ritonavir. On the other hand, almost 50% of patients when etravirine was administered with darunavir/ritonavir. How-
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Risk Based Strategies for Mitigating Site Quality Issues
Theresa (Tre) Ruth Eisenberg, Senior Manager, Process Management, Standards and Training
ASTELLAS

FORECASTING & OPTIMIZATION OF THE CLINICAL SUPPLY CHAIN
Examination of Quality by Design (QbD) & Quality Risk Management Approaches for the Clinical Supply Chain
Ken Schiff, Director, Quality Assurance/Quality Risk Management, F. HOFFMANN LA ROCHE

LEAN SIGMA & KAIZEN FOR PHARMA R&D
Building and Managing Through A3s
Terence Bamhart, Senior Director, Strategy and Continuous Improvement
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Luis Rios-Nogales, Regional Medical Director, Head of Latin America Clinical Research Region, AstraZeneca

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available at expected exposure if etravirine is co-administered with drugs that can increase etravirine exposure. Etravirine was granted accelerated approval and was labeled for use in combination with lopinavir/ritonavir with caution for the treatment of HIV-1 infection in treatment-experienced adult patients.

Given a continued public health need to have additional therapeutic options to treat HIV infections, approval of etravirine has allowed effective treatment regimens without limiting the antiretroviral combinations. The availability of PK data in combination with safety analysis was pivotal in providing assurance that etravirine could be approved for use with other antiretroviral agents that may increase etravirine exposure.

Case study 2. Oral paricalcitol (ZEMPLAR®) capsule is approved for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD), stages 3 and 4. The sponsor conducted three clinical trials in stage 5 CKD patients to seek approval for oral paricalcitol. Paricalcitol dose was based on baseline intact parathyroid hormone (iPTH) level and the dose was selected to be iPTH/60 µg. The indication was not approved due to high-observed hypercalcemia rates (at that time defined as two consecutive elevations of Ca >11 mg/dL). The sponsor developed models to characterize the relationship between plasma paricalcitol and the measures of efficacy and safety such as iPTH, serum calcium (Ca) and serum phosphorous. The sponsor later conducted a new trial with lower dose (initial paricalcitol dose=iPTH/80 µg), which was projected using the exposure-response model developed for the three failed trials, to seek the same indication in patients on hemodialysis (HD) or continuous peritoneal dialysis (CPD). The proposed and tested paricalcitol dosing regimen (dose of iPTH/80 µg for HD and CPD patients with serum Ca <10.5 mg/dL) was effective in decreasing iPTH levels while the rate of hypercalcemia (now defined as two consecutive elevations of Ca>10.5 mg/dL) remained high and was driven by CPD patients. The agency issued an approvable letter and recommended the sponsor pursue a new iPTH based dosing regimen to obtain efficacy and safety information from a new clinical trial.

Regulatory question: Can an optimum dosing regimen be derived for CKD stage 5 patients on HD or CPD that...
Regulatory Challenges in Global Biosimilars Drug Development

February 22, 2012 at 10:00 AM EST; 4:00 CET

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EVENT OVERVIEW:
Regulations for biosimilars are currently evolving in Europe, the United States and many emerging countries. Europe has been in the forefront of biosimilar regulation since 2001 when the EU created a pathway for the approval of biosimilars. Companies seeking to establish a point of entry to or maintain a position within the biosimilar marketplace must first identify the requisite regulatory requirements for every intended market. As guidelines and pathways around the world continue to mature, the complexity of this exercise cannot be understated. This process needs to follow a logical step-wise progression to ensure that, where possible, a global development plan can be developed to satisfy regulators in each potential market. The regulatory and commercial considerations are the primary drivers for successful biosimilar development, because speed-to-market is critical.

In terms of the biosimilar regulatory process, each country is on its own maturity curve. For countries with still-evolving regulatory pathways and guidelines, companies need to be aware of where they currently are in the evolution, and then anticipate possible likely outcomes based on the existing regulations and past experience. Regulatory strategies must address product, indication and market-specific requirements. This seminar will review the most important regulatory challenges facing global biosimilar development programs at this time and discuss possible considerations that companies can adopt to navigate the evolving landscape.

Key Learning Objectives:
After attending this webcast, participants will be able to:
- Describe and highlight the differences in the current status of biosimilars regulations in the U.S., Europe and Asia Pacific.
- Explain how scientific challenges affect regulators and the companies seeking approval for biosimilars.
- Discuss the EU experience with biosimilars and what it may mean for companies seeking approval in the U.S. and Asia Pacific.
- Identify future developments and ongoing regulatory challenges as biosimilars are introduced in the U.S.

Who Should Attend:
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- VPs of Clinical Development
- Directors of Clinical Operations
- Therapeutic Area Leaders
- Program & Clinical Study Managers
- Directors of Outsourcing & Procurement

Presenters
Robert G Heard Ph.D.,
Vice President,
Biosimilars Development,
PRA

Rodeina Challand,
Executive Director,
Biosimilars Development,
PRA

Moderator:
Lisa Henderson, Editor in Chief, Applied Clinical Trials

For questions, contact Jamie Carpenter at jcarpenter@advanstar.com
balances efficacy and safety, alleviating the need of a new clinical trial? An exposure-response model was developed for efficacy (two consecutive serum iPTH measurements decreased by 30% from baseline) and safety (two consecutive serum calcium measurements over 10.5 mg/dL; hypercalcemia) using pharmacokinetic and clinical response information from the three earlier conducted clinical trials in stage 5 CKD patients with iPTH/60 dosing regimen. The model was validated using an external dataset from the current clinical trial (lower dose: iPTH/80) and was able to predict the efficacy outcome (82.6% predicted versus 87.9% observed) and the hypercalcemia rates (2.0% predicted versus 1.6% observed) that were observed in the trial. However when the results were stratified by HD and CPD patient type, it was evident that hypercalcemia was higher in CPD patients compared to HD patients (0% in HD vs. 21.1% in CPD patients). Lowering of dose maintained acceptable efficacy and resulted in lowering of hypercalcemia. However, the predicted hypercalcemia rates in CPD patients still remained unacceptably high (31.4%). Simulations with switch–dosing schemes, starting with an initial low dose (iPTH/80 μg) for up to eight weeks followed by a higher dose (iPTH/60 μg) for up to 48 weeks did not provide either significant lowering of iPTH or hypercalcemia rates. Further exploration of the exposure-response model revealed that the higher baseline serum Ca levels as well as a higher potency for calcium synthesis drove the differences between CPD and HD. Hence, the lowering of paricalcitol dose alone did not result in lowered hypercalcemia rates in CPD population. Modifying the inclusion criteria to restrict the therapy to patients with lower screening calcium (Ca <9.5 mg/dL) was found to further decrease the hypercalcemia rates in both HD and CPD patient population without compromising efficacy (Table 4).

Zemplar capsules were approved for use in stage 5 CKD patients on HD or CPD without additional clinical trials. The dosing regimen information derived via exposure-response modeling and simulation was included in the label. 9

The pharmacokinetic information collected in the late phase clinical trials was vital in deriving the dosing regimen and alleviating the need of any additional clinical trials.

Case study 3. The sponsor sought approval for an orally administered prodrug, prasugrel, an inhibitor of platelet activation and aggregation for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes. Bleeding is the major risk component evaluated while considering the risk/benefit profile of these anticoagulants. The sponsor proposed a 60 mg QD loading dose followed by a 10 mg QD maintenance dose. A reduced maintenance dose of 5 mg QD for patients with body weight (BW) <60 kg or age ≥75 years was proposed to mitigate the increased risk of bleeding. The sponsor conducted one single Phase III trial to support the indication. Pharmacokinetic data was collected for the active metabolite of prasugrel from some late phase clinical trials (Phase II dose selection trials) but was not collected in the Phase III trial.

Regulatory question: Is the proposed dosing regimen for specific populations (BW <60 kg or age ≥75 years) adequate? Exposure-response pooled-analysis conducted for bleeding using the data from six clinical pharmacology studies provided by the sponsor indicated a trend of increased bleeding with higher exposures of the active metabolite of prasugrel (Figure 2, left panel). Population pharmacokinetic analysis using the data from late phase clinical trials demonstrated weight as the major covariate affecting clearance such that patients with lower body weight had lower clearance and hence higher exposures. Age did not affect exposures after accounting for differences in weight. Specifically, patients with BW <60 kg were at increased risk of bleeding based on the AUC cutoff established in the exposure-bleeding relationship (Figure 2, right panel). Data from the Phase III trial showed that the risk for Thrombolysis in Myocardial Infarction major bleeding with prasugrel was higher in lower body weight (BW <60 kg) group (Hazard Ratio: 3.05 (2.01–4.62), p < 0.0001) compared to patients with higher body weight probably due to higher exposures. It was also seen that efficacy was similar across different weight groups.

Pharmacokinetic simulations were conducted to show that the dose adjustment to 5 mg QD in patients weighing <60 kg will shift the exposures in the majority of these patients from the upper quartile to lower quartile of those seen in patients with body weight >60 kg (Figure 3). Thus, reduction of maintenance dose from 10 mg QD to 5 mg QD in patients with body weight <60 kg is acceptable.10

**Figure 3.** Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight <60 kg will result in exposures predominantly corresponding to the lower two quartiles of those expected with 10 mg MD in patients with body weight >60 kg.
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Age ≥75 years was an independent predictor for increased risk of primary composite efficacy endpoint (cardiovascular disease/non-fatal myocardial infarction/non-fatal stroke) and major bleeding. In patients age ≥75 years, the efficacy of prasugrel was numerically better than clopidogrel with a similar risk for bleeding. Furthermore, after adjusting for body weight, the exposure of active metabolite of prasugrel did not increase with age. Hence, dose reduction in elderly patients due to age alone is not justified.

The dose recommendations requiring lower maintenance dose in patients less than 60 kg were included in the label. No dose reduction in elderly patients (≥75 years) was recommended.21

Lighter patients were at higher risk of bleeding. The availability of PK information in the late phase clinical trials helped establish the body weight-exposure and exposure-bleeding relationship suggesting that lowering the dose in lower body weight patients (BW <60 kg) will reduce exposures thus reducing the chances of bleeding. At the same time, there will be no loss in efficacy as exposures in these lighter patients (<60 kg) receiving 5 mg would be similar to higher body weight patients (≥60 kg) receiving the 10 mg dose. In summary, the PK and safety information in the late phase clinical trials along with efficacy information from the Phase III trial provided evidence to recommend an optimum dosing regimen in a patient population at higher risk of bleeding.

Case Study 4. The sponsor sought the marketing approval of lacosamide for the indication of the treatment of epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older. To support the efficacy claim, the sponsor conducted three pivotal trials to evaluate dose ranging from 200 mg to 600 mg. Due to large variability in PK, the dose response relationship was not apparent. Therefore, exposure-response analysis was performed.

Regulatory question: What is the optimum dose of lacosamide in treating patients with partial seizure?

The exposure-response relationship for lacosamide in treating patients with partial seizure was established in the subset of patients in three pivotal clinical trials where PK samples were available and baseline seizure was fully characterized. Our analyses focused on observations at two critical time points (i.e., by the end of titration phase and by the end of maintenance phase). The exposure was defined as AUC over a dosing interval of 12 hours at a steady state. The response was defined as a change from baseline of the average daily number of partial seizure.

An $E_{\text{max}}$ model described the exposure-effectiveness relationship, as shown in Figure 4. The response curve started to flatten out beyond the median exposure of the 400 mg dose. Therefore, the 600 mg dose does not appear to provide additional benefit compared to the 400 mg dose.22

Based on the exposure-response analysis, the dosage and administration section of lacosamide package insert was updated. The following language was included:23

VIMPAT can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day, based on individual patient response and tolerability. In clinical trials, the 600 mg daily dose was not more effective than the 400 mg daily dose, and was associated with a substantially higher rate of adverse reactions.

This conclusion could not have been arrived at based on the effect at each dose alone, owing to the overlapping PK across the doses. The dose-response curve appeared flatter than the exposure-response curve.

Discussion

The internal survey of NDA/BLAs submitted between 2002 and 2008 highlights the value of collecting PK in late phase clinical trials in approval and labeling related decisions. In most cases, sparse sampling with or without rich PK sampling in some patients was conducted. Adequate design and informative sampling for PK data can serve as a useful surrogate for an individual’s exposure. Sparse PK samples were used mainly for population analysis to identify important covariates in the late 1990s. The current survey indicates that FDA and industry are employing PK in late phase clinical trials to support evidence of
effectiveness, derive dosing regimen not directly studied in trials, and identify at-risk patients. About 56% (39/70) of the submissions with PK data in late phase clinical trials contributed towards approval related decisions. Most importantly, among these 39 submissions, exposure-response modeling alleviated the need for additional trials for 11, leading to reduced drug development cost and time. Our internal experience suggests that almost half of the submissions utilized the PK data to conduct exposure-efficacy analysis. This is a significant return on investment given the amount of time, money, and resources spent by a pharmaceutical company required to bring a drug candidate to market compared to the cost of collecting PK.

The etravirine case study represents a scenario where the PK data was useful in assessing the risk profile in a specific target population and allowed for the approval of etravirine with other anti-retroviral agents without any additional trials. In the case of paricalcitol, the dosing regimen was modified based on the exposure-response relationship and thus alleviating the need for additional trials. Oxcarbazepine was approved for treating partial seizures, as a single agent, in pediatrics four years and older based on pharmacometric bridging of exposure-seizure reduction relationships in adults and pediatrics receiving combination treatment. If the sponsor had not collected PK data in the combination use trials, such an approval would not have been possible. Other anti-epileptics are following a similar path. The primary basis for the approval of argatroban dosing in pediatrics was derived based on the exposure-anti-coagulation relationship. Again, without the PK data a similar regulatory decision might have not been reached. Further, PK data identified patients with compromised hepatic function as at-risk population requiring a different start dosing. The collection of PK data, for both cyclosporine and everolimus, in the first everolimus trial in heart-transplant patients allowed derivation of a dosing regimen with reduced risk of nephrotoxicity. The sponsor tested that simulation-derived regimen in renal transplant patients and found the risk of nephrotoxicity was as predicted. Everolimus is approved for prophylactic treatment of renal transplant patients. Transplant trials are challenging to conduct, and without the PK data, exploration of alternative dosing schemes for the next trial would not have been possible.

Labeling decisions were affected for 87% (41/47) of the submissions. For prasugrel, PK information was vital in figuring out that increased bleeding in lower weight (<60 kg) patients was due to an increase in exposure. Hence, a lower dose was approved for these patients. More importantly, the lower dose would not result in loss of efficacy since PK would be within the effective exposure-range. Sponsor use population analyses based on sparse PK information in late phase clinical trials that provides most of the PK character-

ization for biologics. Eli Lilly reported that gemcitabine’s PK evaluation was based on sparse PK sampling in late phase clinical trials. Pfizer noted that exposure-response analysis using the PK data from Phase III trials allowed alleviating the need for additional efficacy trials for gabapentin. Its labeling states that pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence. Hoffman La Roche evaluated the integration of pharmacokinetic and pharmacodynamic principles in clinical development by looking at 18 projects in their development portfolio. Pharmacokinetic and pharmacodynamic principles were applied in every project independent of development phase and therapeutic area with selection of dosage for the clinical studies being their most important application. Furthermore, use of these principles resulted in significant time savings up to several months in many projects.

For nine NDAs, PK data were not collected in late phase trials. For several of these, PK data might not have added much value. For example, WelChol (colesevelam hydrochloride) is a resin for local GI action that is not systemically absorbed. Another NDA was for an investigational drug with very short half-life. PK data were not collected in the registration trials for tetrabenazine. As tetrabenazine’s major metabolites (α-dihydrotetrabenazine and β-dihydro-tetrabenazine) are further metabolized via CYP2D6 and poor metabolizers have higher exposures (3- and 9-fold, respectively), it might have been valuable to collect PK data. However, one of the trials involved dose titration using doses of 12.5 mg to 100 mg in each patient providing a rich individual dose-response. This dose-response provided the confirmatory evidence for effectiveness and alleviated the need for additional efficacy trials. For six NDAs, PK information was collected but did not directly affect labeling decisions. One of these NDAs was for a post-marketing safety study for ranolazine. It is challenging to speculate the impact if PK data were collected.

The results of the external survey suggest that one of the main drivers to collect PK data in late phase clinical trials is to provide evidence of effectiveness. Practicality or feasibility was the top reason given for not collecting PK data in late phase trials. However, based on our internal survey, 70 submissions that include well over 120 trials across various therapeutic areas had PK data collected. In fact, some of the trials involved collecting sparse PK data from thousands of subjects (e.g., Prasugrel). It’s likely that the sponsors of these trials realized the value of collecting PK and/or implemented efficient clinical trial practices that allow them to collect PK data.

Spending time, money, and resources to collect PK information in late phase clinical trials is a significant return on investment for the pharmaceutical industry. It provides valuable information that can help in high-level approval related regulatory decisions and can also be useful in
providing valuable labeling instructions, which otherwise would not be possible. We present results from two surveys (internal and external) that support the argument of collecting PK data in late phase clinical trials. We hope that the regulatory perspective presented here provides evidence to support and encourage collection of PK data in late phase clinical trials. This can reduce drug development cost and time, helping safe and effective drugs reach the target population in a timely manner and also provide the most appropriate labeling instructions for practicing physicians.

References

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People

- Southern Research Institute (Birmingham, AL) announced that Damon Papac, PhD, and Joseph Murphy, PhD, have joined the not-for-profit research organization to lead two key departments within its Drug Development Division, a technology group that primarily provides contract preclinical drug development services for the pharmaceutical industry and government clients.
- Premier Research Group (Philadelphia, PA) has appointed Etienne Drouet to the position of Executive Director, Oncology Europe.
- ACR Image Metrix (Philadelphia, PA) has appointed Paul Ellenbogen, MD, Chairman of the ACR Image Metrix Board of Directors, Partner at Radiology Associates of North Texas; Jonathan Lewin, MD, Chairman, Department of Radiology and Radiological Science at Johns Hopkins University and Radiologist-in-Chief at Johns Hopkins Hospital; and Harvey Neiman, MD, Chief Executive Officer at ACR Image Metrix and Executive Director of American College of Radiology. In addition, Donald Rosen, MD, Co-Founder of RadPharm, Inc.; Samuel Broder, MD, Former Vice President and CMO of Celeria; Carolyn Melzter, MD, Chair of the Department of Radiology at Emory University School of Medicine; and Joel Morganroth, MD, Chief Scientific Officer at ERT, have been appointed to the board of directors.
- invivodata (Pittsburgh, PA) has appointed Wolfgang Summa, PhD, Vice President of Worldwide Operations. Working out of invivodata’s headquarters in Pittsburgh, Summa will be responsible for managing the successful implementation of invivodata’s ePRO solutions in clinical trials around the world.
- Clinipace Worldwide (Morrisville, NC) announced the addition of John Larus as Executive Vice President of Clinical Operations, to its growing team of clinical development experts.
- Covance has appointed Raymond Kaiser, PhD, as the new Global Science Leader and Vice President for Biotechnology Services. Kaiser will replace Carl Martin, PhD.
- John Potthoff, PhD has been appointed as Theorem Clinical Research’s (King of Prussia, PA) President and CEO. He succeeds James M. Pusey, MD, who has been elevated to Executive Chairman to the Board of Directors. In addition, Adam Serody (King of Prussia, PA) has joined the company as Vice President, Global Business Development and Marc Hoffman, MD, has joined the company as Senior Vice President and General Manager for its newly formed Pharmaceutical Development Business Unit.
- Christian Tucat has been appointed Vice President and General Manager, Europe, Middle East, and Africa.
- With more than 18 years of experience, Li Liu, PhD, has joined Frontage Laboratories (Exton, PA) as Executive Director, Biometrics, responsible for Biometrics Services.
- Bringing 23 years experience within the pharmaceutical and CRO industry, Steve Cutler, PhD, has joined ICON (Dublin, Ireland) as Group President, Clinical Research Services.
- BioPharm Systems (San Mateo, CA) has named Rudolf Coetzee as Director of Business Development for the Europe, Middle East, and Africa region.
- DaVita Labs (Fort Lauderdale, FL) has hired Leslie Mirani as the company’s new Vice President and General Manager.

Acquisitions

- Quintiles (Research Triangle Park, NC) has acquired Outcome Sciences, Inc., a privately held outcomes research firm headquartered in Cambridge, MA.
- Aptiv Solutions (Reston, VA) has acquired SRA Global Clinical Development, the CRO division of SRA International, Inc. based in Durham, NC, with offices in Paris, France and Milton Park, England.

Alliances

- INC Research (Raleigh, NC) and SAS (Cary, NC) are working together to improve clinical development risk management and achieve targeted product profiles through analytics. They will offer biopharmaceutical...
customers an integrated suite of tools to increase decision-making speed, efficiency, and flexibility.

- ICON (Dublin, Ireland) and Empire Genomics (Buffalo, NY) announced the formation of a strategic alliance to develop a service portfolio tailored to the development of personalized medicines.
- TAKE Solutions (Princeton, NJ) has partnered with MENE Research (Istanbul, Turkey) and together will cater to the Drug Safety requirements of Middle East, Europe, and West Asian countries.
- Alquest (Northwood, OH) has become the first organization to join MedNet Solutions’ (Minnetonka, MN) iMedNet CRO Partner Program.
- Boehringer Ingelheim (Ingelheim am Rhein, Germany) has awarded Patheon (Toronto, Canada) two projects with combined revenue of more than $18 million over a three-year period. The projects are both fixed-dose combination drugs in development for the treatment of the growing population of type II diabetics.

**Awards**

- Exco InTouch (Sawbridgeworth, UK) has received the European Outsourcing Awards held in Frankfurt. Exco InTouch has been honored with the accolade of “Best eBusiness/IT Strategy,” which recognizes Exco InTouch’s collaboration with Pfizer.
- Alquest (Northwood, OH) has become the first organization to join MedNet Solutions’ (Minnetonka, MN) iMedNet CRO Partner Program.
- Boehringer Ingelheim (Ingelheim am Rhein, Germany) has awarded Patheon (Toronto, Canada) two projects with combined revenue of more than $18 million over a three-year period. The projects are both fixed-dose combination drugs in development for the treatment of the growing population of type II diabetics.

**New Facilities**

- Eurofins Global Central Laboratory has opened a new Central Laboratory in Bangalore, India.
- Almac has announced the expansion of its Pharmaceutical Development services with the creation of a new facility at its UK headquarters in Craigavon.
- ICON’s (Dublin, Ireland) resourcing division, DOCS, has expanded in Europe by opening four new offices in Milan, Italy; Budapest, Hungary; Brussels, Belgium; and Berlin, Germany.

**Products**

- Cmed Technology (New Providence, NJ) has launched Timaeus Guided Trial Builder, a new product that introduces a different approach to reduce the time and effort required to start up electronic trials.
- Almac (Craigavon, Northern Ireland) has released its new forecasting platform, COMPASS, which has been designed to improve the accuracy and efficiency of the supply inventory process during clinical studies.
March


19-20: Pharmaceutical Quality Assurance and Control, Amsterdam, The Netherlands. Contact: CIQA

19-21: 3rd Annual Clinical Site Feasibility, Selection and Startup, Philadelphia, PA. Contact: ExL Pharma

19-21: 8th Latin America Clinical Trials Conference, Philadelphia, PA. Contact: ExL Pharma

19-21: 3rd Annual Patient Engagement Summit, Philadelphia, PA. Contact: ExL Pharma

19-23: Clinical Science Course for Clinical Research Professionals, Philadelphia, PA. Contact: SoCRA


20: Patient Recruitment and Retention within a Pediatric Patient Population, London, UK. Contact: SMI

21: The Good Clinical Practice Refresher Course, London, UK. Contact: BARQA

21-22: Auditing Electronic Data Capture, London, UK. Contact: BARQA

21-22: Pediatric Clinical Trials, London, UK. Contact: SMI


22-23: Medical Device Good Clinical Practices and Monitoring, Coral Springs, FL. Contact: MRM

22-23: GMP Compliance for Quality Control and Laboratory Operations, Copenhagen, Denmark. Contact: Key2Compliance, +46 8 544 81160, www.key2compliance.com

22-23: CBI’s 5th Annual Clinical Trial Management Systems, Philadelphia, PA. Contact: CBI


26-27: Implementing Quality Systems in Research Environments, Cambridge, UK. Contact: BARQA


27: Introduction to the Principles of GCP, Buckinghamshire, UK. Contact: ICR

27-28: Research Quality Assurance for Good Laboratory Practice, Cambridge, UK. Contact: BARQA

27-29: Auditing for GMP Compliance, Amsterdam, The Netherlands. Contact: CIQA

28: Writing Professional Monitoring Reports, Coral Springs, FL. Contact: MRM

28-29: Preparing Compliant eCTD Submissions, Rockville, MD. Contact: Regulatory Affairs Professionals Society, (301) 770-2920. www.raps.org

29: Audits and Inspections: Preparation and Performance, Buckinghamshire, UK. Contact: ICR

29-30: Advanced Site Management: Finance and Productivity, Baltimore, MD. Contact: SoCRA

29-31: Advanced Quality Monitoring, Coral Springs, FL. Contact: MRM

April

2: Science of Clinical Trials Design, Santa Clara, CA. Contact: UCSC Extension in Silicon Valley

4: Good Clinical Practices, Santa Clara, CA. Contact: UCSC Extension in Silicon Valley

10: Global Conduct of Clinical Trials, Santa Clara, CA. Contact: UCSC Extension in Silicon Valley


ExL Pharma: (212) 400-6240, www.exlpharma.com

ICR: Institute of Clinical Research, +44 1628 899755, www.instituteofclinicalresearch.com

CBI: Center for Business Intelligence, (781) 939-2400, www.cbinet.com


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**Give the Patient a Clear Voice**

I cannot believe FDA did it again. For two years in a row, FDA comes out as the leader, pushing our industry forward. At the end of 2010, we thanked FDA for encouraging us to listen to the patient. This came through loud and clear in FDA’s publication and promotion of their patient reported outcome (PRO) guidance at the end of 2009. PROs are direct reports from the patients that are not interpreted by a health professional. The propagation of PROs across product development programs, and the appearance of new PRO-based labels in the past two years is clear evidence we in the industry are hearing FDA’s message.

In 2011, FDA went yet another step by telling us that there are multiple ways to give the patient a clear voice in clinical research. Specifically, FDA stated that we need to ensure all of our measurements and outcomes, not just PROs, reflect what is happening with the patient. In other words, we need to provide evidence that all of our instruments or tools measure what we think they measure. In FDA terminology, we must ensure that instruments or tools and their related outcome measures are fit for purpose in their context of use.

Specifically, this means that instruments based upon a clinician’s evaluation of a patient (ClinROs), and measures taken by an observer (ObsROs), like a mother reporting about her child, are subject to the same requirements for reliability and validity as PROs. FDA expects that all outcomes assessments (OAs)—ClinROs, ObsROs, and PROs—will meet 21 CFR 314.126(b)(6) requirements that “the methods of assessment of subjects’ response are well-defined and reliable.” The recommendations of how to meet the well-defined and reliable standard are delineated in the PRO guidance. In other words, FDA is using the PRO guidance as the yardstick by which it measures all OAs.

The announcement regarding OAs came during an FDA-sponsored workshop held on October 19, 2011 at the FDA White Oak Campus in Silver Spring, MD. Both FDA and the industry were represented at this one day workshop. Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research, gave the opening address and set the stage for OAs:

“Now clinical trial outcome assessments are one type of drug development tool that we have identified as ripe for improvement. The identification, development, and qualification of new clinical trial outcome assessments is an area that has really not been aggressively pursued by the scientific community, and the lack of—the consequent lack of assessment tools has been impeding, I think, the successful development of new drugs because we really in many cases don’t know how to measure the impacts, both for good and ill, of the drugs that we test in people. And we can do better.”

This challenge from Woodcock also provides opportunity. OAs that are well-defined and reliable can support novel labels for our products, which in turn differentiate them from other treatments. There is now a defined regulatory pathway to novel product labeling.

It is refreshing to see that regulators are prepared to help us in the industry meet the challenges of bringing new products to market, and most important, to create a pathway of success for these products. What do you have planned for 2012, FDA?
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