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ANDRZEJ CZARNECKI
EDITOR-IN-CHIEF

Access to Medicines

From all perspectives, the pharmaceutical sector strives to deliver access to medicines. This statement is differently understood, interpreted, and acted upon by various organizations in different parts of the world. Industry innovations bring new and well known drugs to patients; academia has substantial input into laboratory and clinical development; and regulators facilitate and prioritize legal access for patients as shown in the recently released EMA Roadmap to 2015. In some parts of the world, however, there may be an entirely different understanding of access/availability of medicines. In such places, it may simply mean having or not having a drug to treat a given disease.

Regulatory approaches to the access of medicines are very important and have public health as a priority. Therefore, the concept of benefit/risk is increasingly explored and evaluated through scientific considerations. It is also noteworthy that benefit/ risk, as a concept, has managed to overtake the emphasis on risk (see "Open Forum," Feb 2010), to clearly state that all drugs are developed with efficacy in mind, since if there is no efficacy, even absolute safety is irrelevant for patients. With benefit/risk assessment in place, there are other points to consider in facilitating access to medicines. Some of them, at first sight, seem to present conflicting ideas, such as facilitating access and conditional licensing or introducing effectiveness assessment in many countries before a drug becomes available to patients. These

conflicts can and will be resolved, allowing for the availability of new, high-quality products with a clear benefit/risk profile. It is very helpful to see a statement in the profile of Dr Anne Castot (see this issue's "Profile") that "clearly the feeling is that we are all in it together," in relation to regulators and drug manufacturers. This message, delivered by a renowned regulator involved in drug safety for many years is a true reflection of the combined efforts of all professionals for the benefit of public health. Having a common understanding and goals is crucial in fulfilling the European Medicines Agency's task of delivering new medicines to the market.

A much wider activity is needed in today's difficult economic and scientific conditions to deliver products with appropriate benefit/risk profiles. The present and the future of drugs belong to an era of better scientific cooperation that will include new methods of benefit/risk assessment, as well as an increase in the number of comparative clinical trials. Other regulatory decisions could be helpful in facilitating better access to medicines in more stringent conditions and requirements in licensing of new products. One of the potentially helpful solutions would be a concept that I have been advocating since 2002, ie, the broader involvement of regulators in the design of curricula for physicians and other health care professionals.

No company activity would or could be as effective and achieve the right level of success in disease treatment unless there is a broad basis of understanding of what benefit/risk, risk management, and rational pharmacotherapy mean. Cooperation between regulators and academia could deliver a curriculum for health care providers in clinical pharmacology, pharmacovigilance, and pharmacoepidemiology that would stress the concepts of risk management and risk minimization based on benefit/risk assessments. Future HCPs would therefore be better able to understand the regulators' and companies' requests for cooperation so as to deliver the best for the patients. Such a situation would be very much in line with Dr Castot's statement "that we are all in it together, and the most important objective for us is to deliver new strategies for new products to improve public health."

Introducing better teaching of clinical pharmacology, risk management, and drug safety to improve public health through rational pharmacotherapy and risk minimization could as well, in everyday practice, help to reduce the number of avoidable adverse reactions due to older products. This reduction could be accomplished by increasing the understanding of drug use and by providing a better and clearer message to prescribers on sources of information and the need to cooperate with license holders who have extensive knowledge of their products, in risk minimization activities.

As with all issues of the *Global Forum*, I encourage everyone to choose relevant articles from our "Best Practices" section and specifically to look at the articles on comparative effectiveness research, the main theme of this issue. The six articles cover a range of issues and provide timely information for readers in all disciplines. This section was edited by Professor C. Daniel Mullins from the University of Maryland School of Pharmacy. We all thank him for taking the role of guest editor and providing a very interesting series of articles for us. ■

Voices in Harmony Spring from Monaco

DIA Vision

DIA is the global forum for knowledge exchange that fosters innovation to raise the level of health and well being worldwide.

JEFFREY W. SHERMAN

The April *Global Forum* provides a unique moment in DIA's annual calendar to reflect on the success of our recent EuroMeeting, our flagship offering in Europe held each spring, and to consider how we can incorporate the knowledge from the EuroMeeting into our future plans.

I was thoroughly impressed by the dialogue generated in the EuroMeeting's opening plenary session, a debate on the provocative motion, "The process to develop new medicines and bring them to patients is neither efficient nor effective." The experts assembled for this debate represented leadership from the pharmaceutical industry and the European Medicines Agency (EMA), and embodied what DIA does best: Provide an invaluable neutral forum to bring together individuals from different domains to exchange vital information and discuss current issues related to health products, technologies, and services with all of us.

These discussions also embodied DIA's global perspective. Biopharmaceutical, medical device, and regulatory professionals from around the world who live and work in different geographic and political circumstances face many common questions and challenges. Several EuroMeeting sessions, as well as a group of articles in this issue of the *Global Forum*, for which I would like to thank section editor Dr. C. Daniel Mullins, illuminate comparative effectiveness research (CER) and health technology assessments (HTA), two related and relatively recent initiatives that will only grow more important in the context of the current economic and legislative environment. Incorporating and advancing new topics such as CER and HTA into our educational programs and publications is a example of how we will support our expanded, updated Vision and Mission. CER and HTA will also serve as major topics at our upcoming Annual Meeting in Washington, DC.

CER and HTA have an impact on all of us, our families, friends, and colleagues as "end users," or patients who use the products that we develop, review and approve, deliver, market and regulate. In Monaco, we proudly celebrated the fifth anniversary of our EuroMeeting Patient Fellowship program, which promotes and financially supports the participation in our flagship European educational forum by representatives of patient organizations from Europe and elsewhere. The list of countries from which these advocates came this year includes Belgium, Canada, Croatia, France, Germany, Greece, Hungary, Italy, Lithuania, the Netherlands, Poland, Romania, Sweden, Spain, and the United Kingdom.

Whether the location is the annual EuroMeeting or Annual Meeting, one of our upcoming meetings or educational programs in China, India, Japan, Latin America, online or elsewhere, one critical dynamic remains constant: How important it is for everyone involved with DIA, our members, volunteers, thought leaders and elected leadership, and the numerous international and national scientific, regulatory, and professional organizations with whom we develop and present these programs, to keep working together toward our shared vision – to foster innovation to raise the level of health and well-being worldwide. ■

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The *DIA Global Forum* provides a multidisciplinary,neutral forum for communicating information related to drug development and lifecycle management on a global basis. The *Global Forum* disseminates content that is relevant to members' professional experiences, including international industry and regulatory updatesandnewsoftheassociationanditsprograms.Themagazine is circulated six times a year as a benefit of DIA membership.

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Hot Topics in Monaco

PAUL POMERANTZ

This time of year, the weather in Monaco can be chilly. But make no mistake, it was hot this month in the Grimaldi Forum, the site of the 22nd Annual EuroMeetng which ended on March 17. It was, in every way, outstanding. The credit for this energetic and innovative conference belongs to its co-chairs: Bruno Flamion and Kerstin Franzen and the Program Committee. I would like to reflect on two key learnings from the program and their implications for DIA from a global perspective.

First, the EuroMeeting, through the ultra successful Patient Fellowship program, allowed for the voice of the patient to be prominently heard. This year, thirty-five individuals representing patient organizations were awarded either full "scholarships" to attend or have their registration fees waived. In return, these patient "experts" contributed their unique perspectives to many panels and sessions. As part of DIA's renewed commitment to providing patients with the same forum offered to all professionals involved in the discovery, development, and life cycle management of pharmaceuticals, medical devices, and related products, this year's EuroMeeting featured an entire theme dedicated to "The Informed Patient."

It was timely that immediately following the EuroMeeting, the March 11 issue of the *New England Journal of Medicine* featured as a lead perspective, "The Missing Voice of Patients in Drug-Safety Reporting," by Ethan Basch of Sloan Kettering Memorial Cancer Center. Dr. Basch reported on the emerging science of patient-reported outcomes and its potential to more effectively identify and report benefits and risks of therapies.

Clearly, the "voice of the patient" is an important one for DIA, complementing our "traditional" constituencies of industry, regulators, and academia. The patient perspective is gaining increasing credibility in this age of health reform, when nations around the world are seeking to balance access, quality, and cost. At the end of the day we're all patients, so we can appreciate their many insights, including:

- Advocacy for innovation to address neglected diseases
- Developing mechanisms to address patient-reported outcomes
- Facilitating more relevant and complete information to patients in labeling and other venues
- Helping to facilitate a stronger partnership between patients and providers to promote more engaged and informed decision making
- Playing a key role in setting the methodology, agenda, and use for outcomes research

Part of the agenda for our June Board meeting will include "Patient Groups and DIA" that will include presentations by leaders of EURORDIS (European Organization for Rare Diseases) and the National Health Council. During this meeting, we will consider how to further engage the patient voice in our programming, membership and governance. I will report on this discussion in the August issue of the *Global Forum.*

From its inception one year ago, the *Global Forum*, in conjunction with CiSCRP, has featured an article that highlights the viewpoint of patients in its "Patient Perspective." column. This month's article depicts the emotional story of John Crowley, subject of the movie *Extraordinary Measures* and the quintessential spokesman for families seeking life-saving therapies, and his search for a cure for Pompe disease, which affects his two children.

The second key learning from the EuroMeeting centered around health technology assessment (also known in the United States as comparative effectiveness research), which was introduced in the opening plenary. Moderated by Professor Stuart Walker (Founder, CMR International Institute for Regulatory Science), the plenary debate featured presentations by Thomas Lönngren (Executive Director, European Medicines Agency), Eddie Gray (President, Pharmaceuticals Europe, GlaxoSmithKline), Eric Abadie (CHMP chair and General Directorate of the French Agency, AFSSAPS), and Richard Bergström (Director-General, Swedish Association of the Pharmaceutical Industry) addressed the thesis, "The process to develop new medicines and bring them to patients is neither efficient nor effective." The discussions covered the increasing cost of development and the opportunities posed by personalized medicine, regenerative medicine, drug device combinations, neglected diseases and preventive vaccines. Most important however, was the insight that the current system of drug development and regulation is no longer sufficient to address the growing demand by governments and payers to integrate considerations of cost benefit with safety and efficacy. While we have harmonized approaches for safety and efficacy on a global basis, systems for health technology assessment diverge greatly, even among the members of the European Union. There is a need for a common language, data standards, and scientific processes to support this.

To paraphrase the speakers, we are using "20th century tools to develop and regulate 21st century products." While product development has historically been tied to the needs of markets, today it must address the need of health systems. Nations are seeking to develop a strategic agenda for health, in which the development of new medicines, and the optimization of current ones, will play a crucial role.

The EuroMeeting represented for me an important microcosm of DIA in that it brought all stakeholders together on neutral ground for meaningful discussion of major issues. It raised two hot topics—the voice of the patient and the integration of technology assessment in the regulatory process—in which DIA can facilitate understanding and progress.

These themes, and many others, will be discussed at the 46th DIA Annual Meeting which will be held in Washington DC, from June13 through 17. Program Chairperson Gaby Danan and the Annual Meeting Program Committee have assembled an outstanding conference that will be kicked off by keynote speaker, FDA Commissioner, Dr. Margaret Hamburg. In addition, we have developed a couple of timely "hot topics" that we are featuring as part of a new "Thought Leader Tuesday." These are:

- Implications of Comparative Effectiveness Research for Health Care Innovation
  Moderater/Keynote Speaker: Jeff Goldsmith (President, Health Futures, Inc.; Associate Professor, University of Virginia)

  Panelists: Paul Pomerantz, MBA (Worldwide Executive Director, DIA)
  Richard Gliklich, MD (President & CEO, Outcome Sciences Inc.)
  Jack Lewin, MD (CEO, American College of Cardiology)
  Mark B. McClellan, MD, PhD (Director, Engelberg Center for Health Care Reform, Brookings Institute)
  Sir Michael D. Rawlins (Chairman, NICE; University of Newcastle, UK)
  David B. Snow, Jr. (Chairman of the Board and CEO, Medco Health Solutions, Inc.)
  Myrl Weinberg (President, National Health Council)

- The New Landscape of Industry-Physician Relations: From Policy to Practice
  Chairman: Arthur L. Caplan, PhD (Emmanuel & Robert Hart Director, Center for Bioethics and Professor of Bioethics, University of Pennsylvania)

  Panelists: Murray Kopelow, MD (Chief Executive, Accreditation Council for Continuing Medical Education)
  Eric G. Campbell, PhD (Associate Professor, Director of Research, Mongan Institute for Health Policy, Massachusetts General Hospital, Harvard Medical School)

This issue of the *Global Forum* contains a special section edited by Dr. Daniel Mullins (University of Maryland School of Pharmacy) on comparative effectiveness research, health technology assessment, and evidence-based medicine. I would like to thank Dr. Mullins for all of his efforts in bringing these fine articles together.

I know you will find this year's Annual Meeting both meaningful and energizing. I look forward to meeting you there. ■

A New Era in Safety and Risk Management

Janice C. Wherry and John D. Balian

In this RMP/REMS era, the ability of pharmacovigilance organizations to provide state-of-the-art risk management planning will depend on creation of an enduring risk management infrastructure through collaborative partnerships within and across organizations.

Introduction

After more than a dozen high-profile marketed drugs were withdrawn over the last decade due to safety-related concerns, there was significant public and governmental pressure to avoid such occurrences in the future. Additional expectations for product safety fueled an expansion and proliferation of postmarketing initiatives and mandates including Vol 9A EU-RMP and FDA (REMS) requirements. While increased interest in safety and risk management is ultimately good news in emphasizing the importance of proactive identification and management of safety risks, there is the potential for risk management planning to become time consuming, costly to enact, delay decisions on marketing applications, or be more restrictive than needed to achieve goals.

In response to the more recent high profile withdrawals due to safety concerns (eg, Vioxx) or prolonged debates regarding widely prescribed drugs (eg, Avandia), the regulators' imposition of additional and more severe postmarketing safety checks and balances, and the stakeholders clamor for "safer" drugs, these efforts sometimes lead to conflicting risk management issues, with significant consequences in time and resources or drug approval delays and/or restriction in use. The pharmaceutical industry is acutely aware and actively engaged in shoring up the resources, talents, and procedures to effectively address these new needs. Safety strategy and risk management planning have become integral to drug development and critical to the postmarketing viability of products. Whether pharmacovigilance organizations will rise to the challenge and emerge as risk management leaders depends on their ability to recognize the implications of the "new era" and translate that knowledge to effectively partner within and across companies.

The need for a new innovative and transformational model of safety and risk management must be considered in the context of drug development trends. We propose a cutting-edge risk management model based on a risk management infrastructure that provides proactive and iterative characterization of the evolving safety profile, supports and sustains risk management planning throughout drug development, leverages newer strategies to enhance assessment of population and individual risk, and creates and maintains strategic partnerships with external stakeholders to advance tools and processes for future risk management communication.

Pharmacovigilance Systems

A best-in-class pharmacovigilance (PV) safety operational and reporting system provides the fundamental framework on which risk management planning is based, namely accurate and timely characterization of the safety risk profile.[1,2] However, there are a number of current challenges in PV reporting including the organization and culture, the increasing volume and complexity of cases, additional regulatory reporting requirements, more frequent co-development

arrangements, increased utilization of remote and contract personnel, and less-than-adequate informatics tools to facilitate higher standards.[1]

The ability to surmount these issues and provide an efficient and self-sustaining PV foundation relies on achieving operational excellence: maintaining stable, large safety databases, automating routine PV processes, flexibility in accessing and reporting individual events and in pooling data for signal detection and aggregate safety reporting, ensuring rigorous training of PV personnel to identify, characterize, and report safety signals, and the overall cost-efficiency of the PV system further enhanced by strategic partnerships and carefully maintained sourcing opportunities.[1]

Exquisite Alignment and Integration of Risk Management

In addition to maintaining solid PV systems, the principles and tools of risk assessment and minimization must become part of systematic planning throughout drug development and postmarketing. The cutting-edge risk management infrastructure includes early and iterative alignment of the safety risk profile, proposed labeling, dossier preparation, launch planning, and RMP/REMS implementation and assessments (Figure 1). Pharmacovigilance experts should lead cross-functional RMP preparation activities that can serve as a focal point throughout drug development. After marketing approval, there must be ongoing alignments of RMP milestones and documents with changes to label and updates to aggregate reports (eg, PADERS, PSURs).

The linkage of pre/post-launch planning and RMP/REMS implementation and assessments deserves special mention. Close partnership between PV-led risk management planning and medical affairs/marketing-led launch strategies and commercialization planning is a relatively new, but required, construct in the risk management infrastructure. For any risk management implementation element, there must be a plan for assessment, and documentation of assessment, of that element.

Contingency Planning

In the new era of risk management planning, where miscalculations could result in significant delays in NDA/BLA/MAA approvals or additional hurdles, PV organizations can no longer afford to develop only the most likely risk management scenarios. Moreover, much is learned from the didactic exercise of considering each risk scenario.

Multipurpose RMP Document

The RMP document itself is an efficient manuscript in that it can be used for multiple purposes in new era risk management planning:

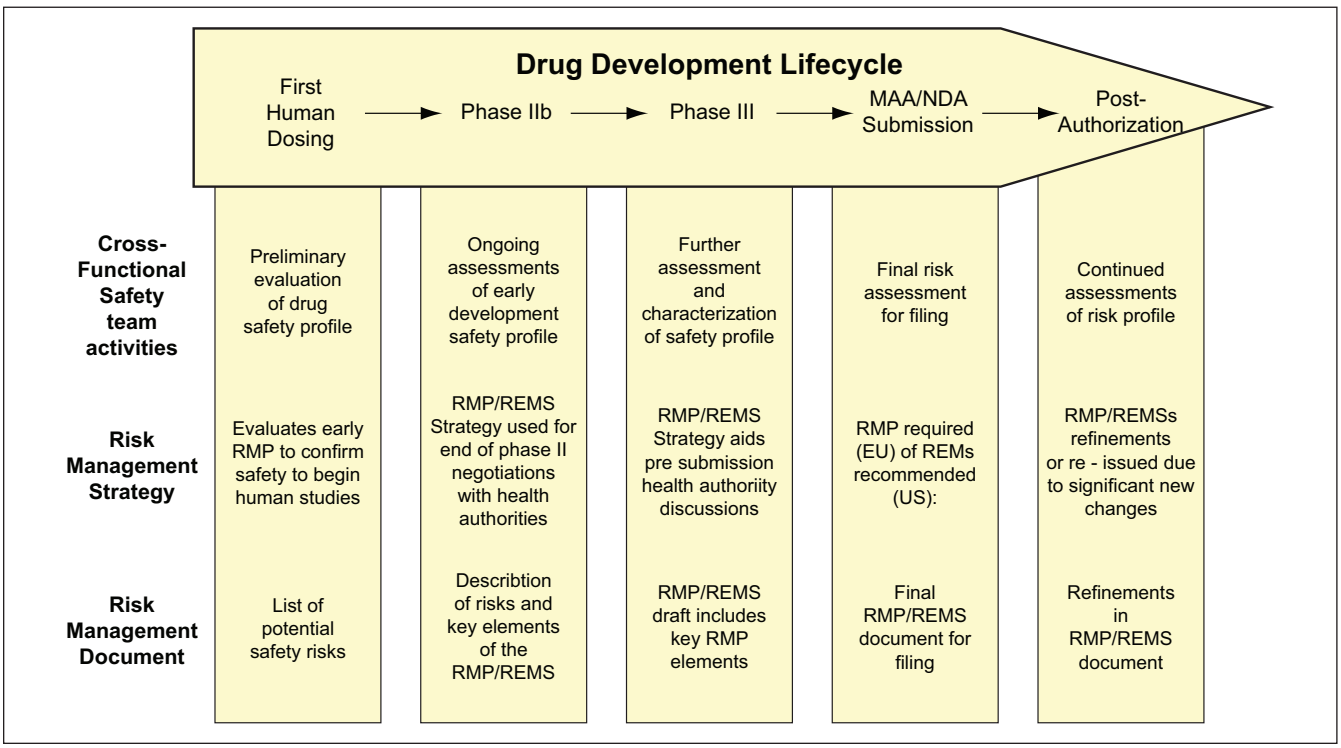


Figure 1. Integrated Risk Management

- Provides an early list of potential safety risks
- Provides a focal point for cross-functional discussions of risk strategy
- Serve as an outline of the proposed RMP strategy for early discussions with health authorities (end of phase 2 or pre-NDA/BLA/MAA meetings)
- Provides an alignment tool for pre/post launch RMP implementation and RMP assessment activities
- Can be submitted not only for MAA submissions, but also can be submitted with NDA/BLA or other health authority submissions to further support the proposed label.

Maintained Risk Management Infrastructure throughout the Postmarketing Period

While the pharmaceutical industry considers the first marketing application for a given product as the main time- and resource-intensive effort, for new era PV risk management planning, the time and resource-intensity and especially the risk management infrastructure, should not diminish in the postmarketing time period. Specifically, additional momentum and alignment are required to address the various postmarketing safety-related requirements across health agencies or even the multiplicity of safety-related postmarketing documents from a given health authority. For example, for the EU-RMP, ongoing alignment is needed with the PSUR, SmPC, and PIL. The requirement for alignment among these documents translates to repetitive examination of all four documents if changes to any are needed.

Given the current flux in REMS requirements and the likely trend towards globalization of risk management requirements in the future, PV organizations should frequently review their risk management plans to assure adherence to current requirements and global needs. Considering the likelihood of class REMS, and the possibility of some form of globally required risk management requirements, PV organizations are well advised to begin now to consider risk management planning for all marketed products.

Enhanced Pharmacoepidemiologic Assessments and Personalized Medicine

While pharmacoepidemiology assesses population-based characteristics, pharmacogenomics evaluates individual and cohort unique responses to drug therapy. There are applications of pharmacoepidemiology and pharmacogenomics technologies that are critical to this new era of safety risk evaluations.

Observational studies give insights into "real-world" populations, enhance our understanding of the natural history of disease, and identify appropriate populations for further clinical study. Drug utilization studies are important in assessment of the effectiveness of implemented risk mitigation strategies at predetermined milestones for EU-RMP and REMS updates.

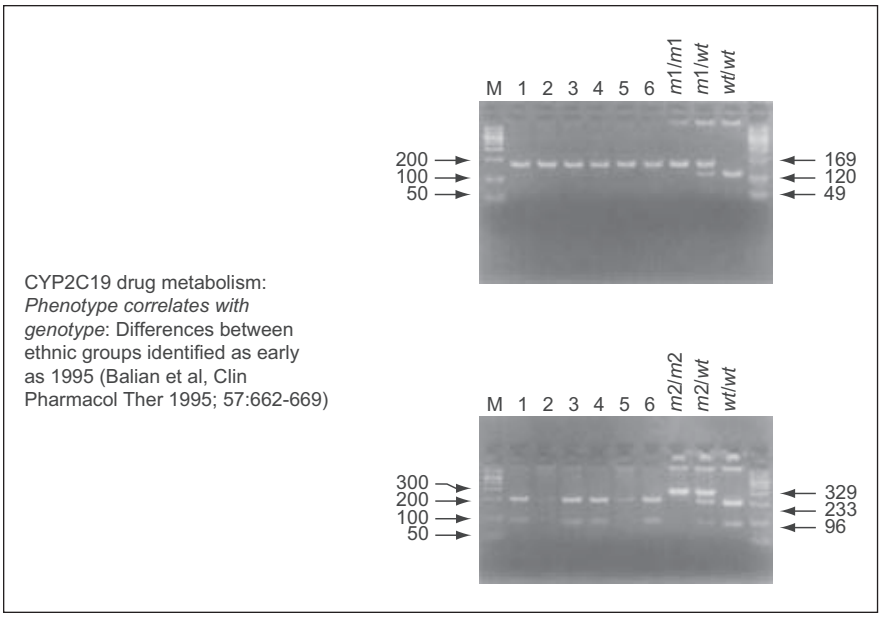
While pharmacogenomic terminology and techniques being employed are relatively new, the concept of interindividual diversity and risk mitigation are not. Indeed, for several decades prior to the recent high profile series of drug withdrawals, individual patient responses, for example, drug metabolism diversity, was linked to distinct genotypes (refer to Figure 2). The hope was that by analyzing such genetic diversity, clinicians would be able to avoid either dose-dependent toxicities or underdosing and lack of efficacy. Although a per-patient (personalized medicine) approach was envisioned at that time, it was not technologically feasible to evaluate appropriate drugs for larger patient populations.

Future applications of genetic profiling include the use of interindividual genetic characterizations to select optimal patient subgroups for treatment. Similarly, genetic profiling may identify specific patient subgroups with less susceptibility to unacceptable side effects, lead to a specifically targeted risk management programs, and potentially allow drugs to remain on the market despite obvious toxicities.

Collaborative Pharmacovigilance

Collaborative partnerships with regulators, industry, academia, public stakeholders are critical to the future of risk management. However, collaborative pharmacovigilance partnerships are still at an early stage. For example, while ICH collaborations have been available for over a decade, and EU-RMP and RiskMAPs requirements have been enacted for over 5 years, it is only relatively recently that EU and FDA have formally collaborated via the Transatlantic Simplification initiative to consider a unified risk management document. There are other collaborations such as OMOP (Observational Medical Outcomes Partnership – public-private partnership) where the benefits will be delayed by the size of the program and long-range goals.

Collaborative pharmacovigilance can lead to advancements in:



CYP2C19 drug metabolism: *Phenotype correlates with genotype*: Differences between ethnic groups identified as early as 1995 (Balian et al, Clin Pharmacol Ther 1995; 57:662-669)

Figure 2. Individual Patient Diversity and Risk Management [3,4]

- Operational simplicity and efficiency
- Safety data evaluation for risk assessment (eg, evaluation of multicompany safety databases of anonymous, pooled trial data)
- Standardization of risk management tools and methods (eg, standardization of data mining algorithms)
- Harmonization of health authority requirements (eg, development of a single harmonized global risk management plan)
- Evaluation of emerging trends in diseases, and determination of background rates of rare events.

For example, given the current lack of consensus in developing FDA guidelines for class opioid REMS requirements, there is an open opportunity for pharmacovigilance leadership in aligning across industry to propose risk mitigation strategies.

Conclusions

In the new era of safety and risk management, we propose a cutting-edge risk management strategy that is not dependent on individual risk management requirements. This risk strategy relies on a risk management infrastructure that provides an enduring framework to proactively, cost-effectively, and iteratively manage safety risks. Such a framework is enhanced by newer technologies of risk assessment and by collaborative pharmacovigilance to advance tools and processes for future risk management communication.

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Check out the Annual Meeting's **Clinical Safety and Pharmacovigilance** track for additional sessions.

The Value and Benefits of the International Conference on Harmonization (ICH) to Regulators

The Common Technical Document as a Common Regulatory Language

Justina A. Molzon

Overview

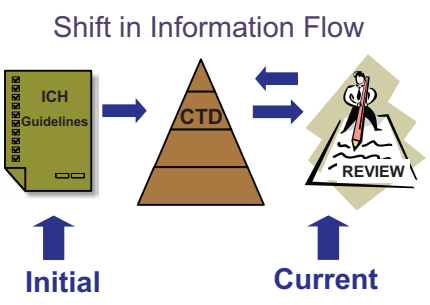
Created in 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. ICH's purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

In 2000, the 10th anniversary of ICH, Dr. Caroline Nutley Loew of the Pharmaceutical Research and Manufacturers of America (PhRMA), wrote a report, *The Value and Benefits of ICH to Industry*. It detailed ICH's creation, procedures, and guideline development in the areas of safety, efficacy, and quality, and anticipated that the Common Technical Document (CTD) would revolutionize the submission procedure for regulatory staff in industry. Dr. Loew characterized the CTD as "offering potential benefits to industry far greater than any other single ICH topic," and predicted that the CTD would afford significant time and resource savings as complex multiple submissions were replaced by a single technical dossier submitted in the three ICH regions—facilitating simultaneous submission and the approval and launch of new drugs. In calling the CTD "a topic whose value to industry cannot be underestimated," Dr. Loew noted that with full incorporation of the CTD and electronic CTD (eCTD), the ICH could then turn its sights to guideline information dissemination to non-ICH countries, yielding additional benefits to both regulators and industry.

Ten years later and in anticipation of ICH's 20th anniversary, the value and direct benefit of ICH to regulators have been realized. Further, the implementation of the CTD in 2003 promoted the involvement of other drug regulatory agencies (DRAs) not initially part of ICH, thereby extending ICH's harmonized approach. The development of the Global Cooperation Group which includes representatives of regional harmonization initiatives (Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Gulf Cooperation Countries (GCC), Pan American Network on Drug Regulatory Harmonization (PANDRH) and Southern African Development Community (SADC), and the newly established Regulators Forum which includes individual non-ICH countries interested in implementing ICH's effort, has also helped incorporate the CTD into regulatory processes creating a common regulatory language that will promote faster access to life-saving treatments to patients beyond the ICH regions.

Shift in Emphasis

ICH's benefit to DRAs resulted when there was a shift of emphasis from input of information by industry to output of information by regulators. This transition was made possible by the development of a common submission format—the CTD—which greatly influenced regulatory review processes, led to harmonized electronic submission and e-review initiatives that, in turn, enabled implementation of good review practices. These activities will ultimately have global ramifications for review and sharing of information between drug regulatory authorities.

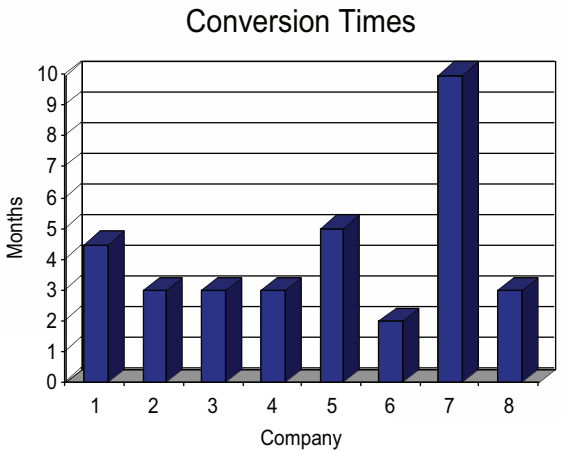


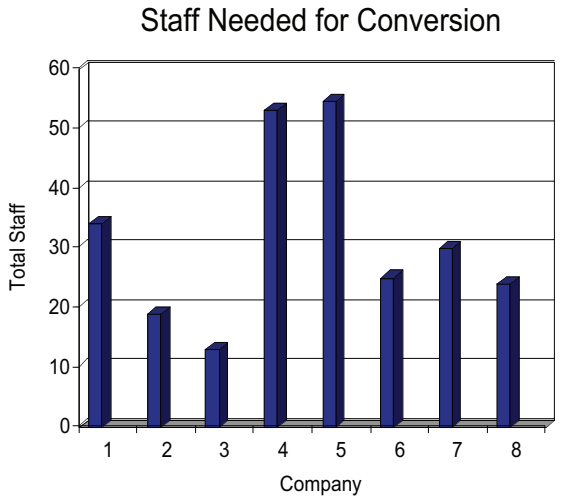
ICH was originally focused on input by industry—the technical submission requirements for pharmaceuticals for human use. Harmonizing the differences in these requirements through ICH guidelines helped industry by reducing development times and resources. To extend the benefits of harmonization, industry proposed assembling these building blocks of information into a consistent harmonized format, referred to as the CTD, which would relieve pharmaceutical companies of the time, workforce, and financial burdens of assembling a submission for one DRA and then having to reformat it for another. This new consistent format also greatly benefited FDA review practices, enabling the agency to establish templates for each of the review disciplines while also promoting more consistent review processes.

Prior to the advent of the CTD, regulatory reviewers would receive an application from one company and spend a year or more ensconced in its review. When the review was completed, they would be assigned another application and would have to re-learn the structure of the application. As a result, review staff were constantly on a learning curve when new assignments were received—time that would have been better served reviewing the information as opposed to simply trying to find it.

When industry proposed the CTD in 1996, ICH regulators were resistant to undertake changes to their submission format, believing it would be too disruptive to the review process. They needed to be convinced that there was value in harmonizing the submission format, and industry was asked to do a feasibility study. That study, conducted in May 1996, evaluated the time it took to convert an FDA new drug application into an EMEA submission, and the reverse. It also evaluated the number and types of staff needed to carry out the conversion of the submission formats.

ICH regulators, impressed with the amount of time and effort involved in the conversion of one regulatory submission into another, agreed that the resources involved could be better used towards more research and development for new drug products. The regulators also realized that these conversions created a delay in submitting an application to the different ICH regions and, in turn, delayed access to new innovative medicines for patients in that region. The result of agreeing to work on a consistent format or table of contents is the ICH Common Technical Document.





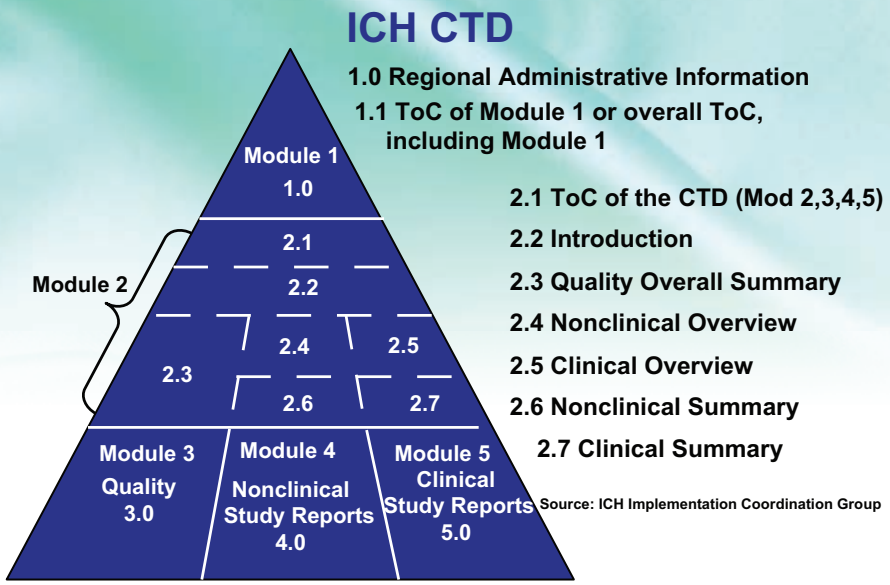
Module 1 is not part of the CTD, but rather represents the regional administrative information specific to each ICH region. Module 2 is a layering of information and includes an introduction, summaries, and overviews. More complete data are contained in modules 3, 4, and 5. Countries can, in effect, focus on modules of interest. If the regulatory authority of a country is not interested in the complete datasets in modules 3, 4, and 5, they can focus on module 1 and module 2, which is what some less-resourced countries are actually doing.

Regulatory Benefits

The benefits of the CTD from the FDA perspective include:

- more easily reviewed applications due to the logical order of the data submitted
- consistent format, a critical factor when assigned multiple applications to review
- consistent output facilitated by consistent format
- easier analysis across applications because of known location of needed data.

The CTD also promotes easier exchange of information between drug regulatory authorities. For a number of years, FDA and the European Medicines Agency have had a confidentiality arrangement in place allowing the sharing of confidential information. This has greatly



increased interactions between the two agencies. These interactions have become more efficient as both agencies are now receiving information in the same format and generally at the same time, facilitating discussion of common concerns as submissions are evaluated.

Lastly, and perhaps most importantly, the CTD facilitated electronic submissions (the eCTD). In the past, drug applications were voluminous and had to be delivered to FDA in trucks due to the sheer amount of paper involved. When the agency first transitioned to electronic submissions, an application was on a compact disc or hard drive. While this certainly helped with transportation and storage issues, it did not necessarily enhance review. We have now implemented the FDA Gateway, which essentially allows an NDA to be sent by email. After being assessed for completeness, a submission is immediately and fully accessible on the reviewer's desktop. With this innovation, industry saves an enormous amount of time by alleviating the need to create and assemble the many pieces of paper that constituted a traditional, paper-based product application, organizing the application, boxing thousands of pages, loading the boxes on a truck, delivering them, and getting them into the FDA system—all of which had to happen before a reviewer could even begin the assessment process.

The eCTD is critical to improving application submission efficiencies as well as reviewers' efficiency. Besides delivering submission material to the reviewer in an expedited manner, the eCTD format has also improved the review process, making it much easier to develop standardized reviewer e-templates and review tools for each of the review disciplines.

The CTD has also helped with the development and implementation of good review practices. What we believe we should evaluate in a review is closely tied to the data we request. As a result, there will be considerable similarity between ICH guidance to industry and what we consider good review practices. Because ICH regions have harmonized much of the information submitted for marketing authorization, ICH regulators could trend towards similar review practices.

In general, good review practices promote transparency and consistency. Transparency of review processes is very important for industry, as well as the public, to understand how regulatory authorities carry out their responsibilities. This is especially important because of the complexity of the disciplines and specialties involved in the review process. We need a consistent approach to evaluating the submissions and expressing conclusions. The CTD and eCTD have helped all of the elements necessary for good review practices to fall into place.

In summary, the CTD format influences the content of the review by imposing a consistent order of information and data. This shapes both the conduct of the review and the presentation of the results of the review, and promotes good review practices and increased efficiency. As more countries utilize ICH guidelines and the CTD format, a common regulatory language could evolve that will further promote interactions between drug regulatory authorities. ■

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A Primer and Beyond f

Nancy R. Katz

The FDA "highly recommends" submission of drug applications in eCTD format. That is, the FDA encourages any pharmaceutical application (for example: an IND, NDA, or BLA) to be written according to the specifications of a template known as the Common Technical Document (CTD), preferring to receive the application in electronic form via an electronic Gateway (hence, "eCTD"). Individuals in the field of drug development take FDA recommendations seriously—especially "highly recommended" recommendations.

Compiling an eCTD-compliant application is a time-consuming and labor-intensive process. Often, the scientists and clinicians who have developed a drug have neither the time nor resources to write the individual documents contained in the application, let alone prepare these documents for electronic submission. Thus, the stage is set for a regulatory writer who can create eCTD-compliant documents and serve as an invaluable member of the drug development team.

Portions of this article are scheduled to appear in Careers in Regulatory Affairs, *edited by Peggy J. Berry, to be published by RAPS in 2010.*

Regulatory writers come from a variety of backgrounds. Currently, no clearly defined education or acknowledged certification is required for someone to be hired as a regulatory writer. However, almost all those employed in the industry hold at least a Bachelor's degree; very often, they have an advanced degree, such as a Masters or PhD, or a professional degree, such as an RN, JD, MD, or PharmD. While many regulatory writers have a scientific background, a significant number of regulatory writers with liberal arts training are highly successful regulatory writers (because they learn, via coursework and on-the-job training, basic concepts and procedures associated with scientific research). Regardless of education and background, successful regulatory writers understand the process of drug development and are thoroughly conversant with CTD structure and guidelines.

To function as an effective member of an eCTD filing team, a regulatory writer must understand the rationale for the eCTD, its requirements and overall structure, and those of the individual documents contained in the CTD. The writer must also create regulatory-compliant, scientifically accurate, clearly written documents that build the case for drug approval. These documents must be internally consistent as well as consistent throughout the application, and they must be linkable to an XML backbone (the technological core of the CTD). Because the content of the drug application is repeated in various formats and in differing contexts throughout the application, the writer must employ strategies that allow effective reuse or repurposing of material. Finally, and not altogether incidentally, the writer must get along with others and function as part of a team.

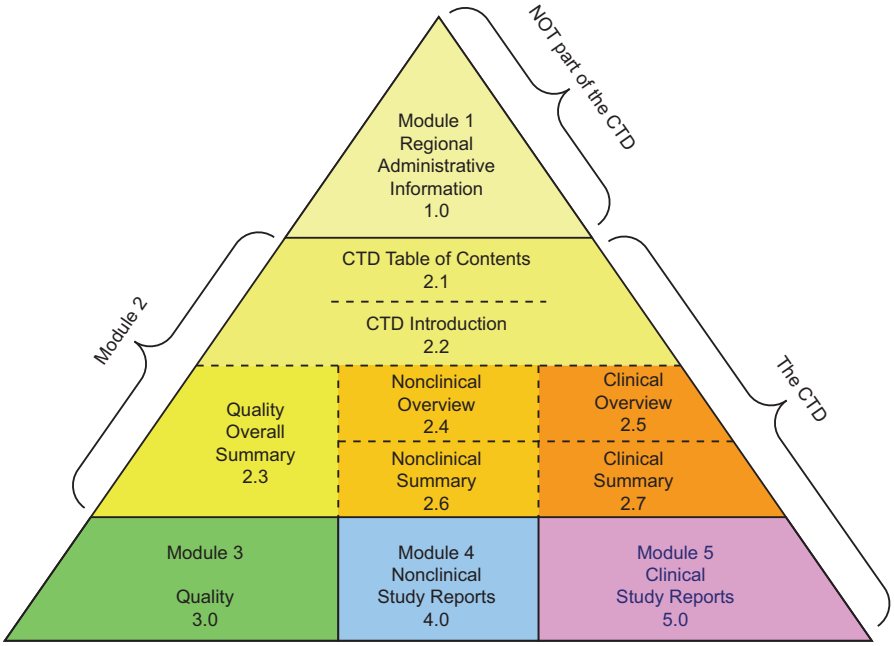
Rationale for the eCTD: Standardization, Transparency, and Efficient Reviews

The CTD template was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (for short, "ICH"; see www.ICH.org). Composed of representatives of regulatory authorities as well as experts from the pharmaceutical industries of three world regions, the European Union, Japan, and the United States, ICH members discuss and recommend processes

TD
for Regulatory Writers

related to the development of pharmaceutical products. ICH's goal is harmonization, or put another way, standardization. ICH seeks agreement regarding the interpretation and application of guidelines and technical requirements for the registration of new medicines. Three desired outcomes of harmonization are 1) reduction of duplicate testing and research; 2) intelligent and economical use of resources (human, animal, and material); and 3) elimination of "unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health."

A drug application submitted in CTD format supports the goal of ICH by eliminating redundant applications: one CTD-based drug application can be submitted to and accepted for review by regulatory agencies in any country of each of the three ICH regions. An electronically based application (that is, an eCTD) further supports ICH's goal by enabling efficient reviews. An eCTD-based application allows reviewers almost instantaneous access to electronic documents and source data, hyperlinked to one another via an XML backbone, and ensures transparency, allowing reviewers to trace the reasoning and data upon which the scientific conclusions of the application are based.



(This graphic was created as a slide for a DIA presentation by Christopher Preston and is reproduced with his permission.)

CTD Structure: The Pyramid and the Greek Temple

The CTD has five sections, referred to as "modules"; traditionally, the modules are depicted as part of a pyramid.

This is a most useful way to conceptualize the CTD. It is helpful to examine the structure from the "base up."

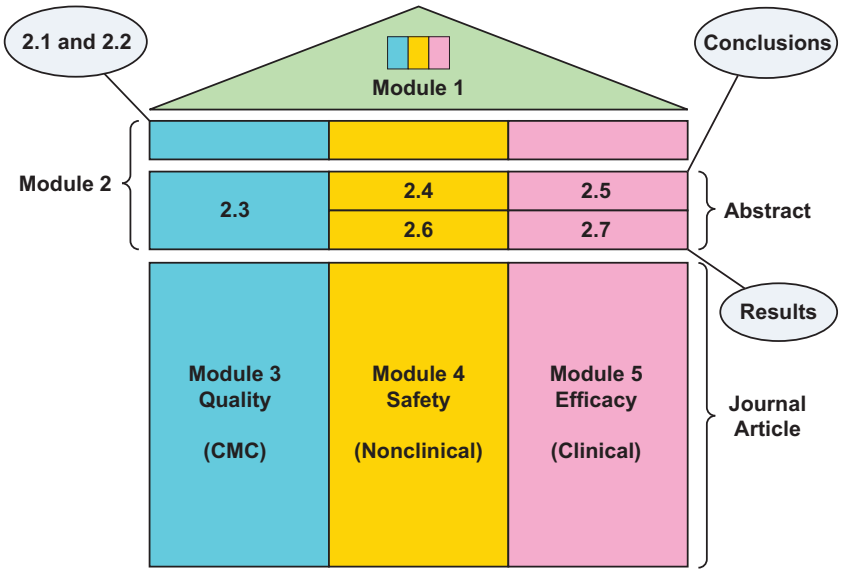
Modules 3, 4, and 5. As the graphic shows, these modules form the base of the pyramid. Module 3, the "Quality" section, contains the chemistry, manufacturing, and

controls (CMC) information. It consists mainly of reports of studies (and associated study protocols) conducted to characterize the pharmaceutical nature of the drug and ensure its purity. Module 4, the "Safety" section, contains nonclinical information. It consists mainly of reports (and associated study protocols) of in vitro and in vivo studies (pharmacokinetic, pharmacodynamic, toxicologic, and immunologic) of the drug in animals. Module 5, the "Efficacy" section contains clinical information. It consists mainly of reports (and associated study protocols) of studies of the drug in human subjects. Included in this module are reports of pharmacokinetic, pharmacodynamic, toxicologic, and immunologic studies in human subjects as well as the phase 1, 2, and 3 clinical studies (including safety narratives for individual study subjects). Other Module 5 documents are the integrated summary of safety (ISS) and the integrated summary of efficacy (ISE) — these are in fact integrated *analyses* of safety and efficacy datasets and differ from the summaries of clinical safety and efficacy found in Module 2 — and postmarketing reports. Modules 3, 4, and 5 contain many subsections not depicted in the graphic; specifications for these modules are provided in the ICH's M4 guidances, listed at the end of this article.

(Some nomenclature is useful at this point: Regulatory writers who write the documents for Module 3 and 4 are sometimes called *technical writers*. Those who write documents for Module 5 are often called *medical writers.* But this distinction is blurring fast, and it is not always useful. A writer who writes documents for any of the CTD modules is properly called a *regulatory writer*.)

Module 2. This module, with its seven subsections, summarizes the content of the three modules at the base of the pyramid and conveys the main, overarching messages of the drug application. Section 2.1 is the table of contents for Module 2 (its function is now subsumed by the XML electronic backbone), and Section 2.2 is a brief introduction to all of Module 2. Section 2.3 summarizes the content of Module 3. Sections 2.4 and 2.6 summarize the content of Module 4, and Sections 2.5 and 2.7 summarize the content of Module 5. Thus, the Module 2 subsections are to the CTD as the abstract of a journal article is to the main text of the article. Specifically, Module 3 is analogous to the body of a journal article describing the quality of the drug, and Section 2.3, the *Quality Overall Summary,* is analogous to the abstract of that article. As in the case of Module 3, Modules 4 and 5 are analogous to the body of a journal article describing the safety (nonclincal studies) and efficacy (clinical studies) of a drug. However, unlike Section 2.3, which summarizes the content of Module 3 in one section, two Module 2 subsections are required to summarize Module 4, and two are required to summarize Module 5. The first layer of summary for Module 4 is Section 2.4, the *Nonclinical Overview*. This section is an overview, comparable to the part of a journal abstract that summarizes the *conclusions* section of an article. The second layer of summary for Module 4 is Section 2.6, the *Nonclinical Summary*. More detailed than Section 2.4, it is comparable to the portion of a journal abstract that summarizes the *methods and results* sections of an article. The same relationship applies to the subsections that summarize Module 5: Section 2.5 provides the overview and Section 2.7 provides the details.

The traditional pyramid of the CTD does not quite capture this concept. To understand the relationship of the Module 2



(This graphic was developed by the author; she has used it in many DIA presentations.)

subsections to their respective modules at the base of the pyramid, it is useful to visualize the CTD as a Greek temple. (You will have to use your imagination here.)

Module 1. This module is not properly part of the CTD. It is an administrative section, consisting of documents specific to the region in which the drug is being submitted (that is, the European Union, Japan, or the United States). Some documents included in Module 1 are the 1) General Investigational Plan, 2) Label (sometimes called the Package Insert [PI]), 3) Risk Management plans, and 4) Clinical Investigator's Brochure (IB). The latter is a document prepared for the investigator. It summarizes current nonclinical and clinical data about the drug under investigation and provides a description of the drug's active and inactive ingredients.

Regulatory-compliant, Scientifically Accurate, Linkable, Re-usable, Clearly Written Documents

Creating a document that meets these specifications can be daunting. Be encouraged by the fact that successful, seasoned regulatory writers are mere mortals who have learned how to do this.

Regulatory-compliant, scientifically accurate documents: Competencies that allow achievement of this standard include knowledge of the following:

- Regulations and guidelines governing the relevant documents in the CTD submission, some of which are listed in the *Resources* section at the end of this article.
- Data and how to work with it: The regulatory writer should understand basic biostatistical principles as well as the underlying principles of programming, data entry, data interpretation, and coding of adverse events and drugs (via specialized dictionaries such as the Medical Dictionary for Regulatory Activities [MedDRA] and the World Health Organization [WHO] Drug dictionary).
- Process of drug development, including principles and practices of clinical studies: The regulatory writer should understand protocol design, both nonclinical and clinical, including the logistics involved in running studies; principles of safety reporting, including reporting of serious adverse events (SAEs); creation of the final study report for a clinical trial; and basic clinical laboratory tests and interpretation of chest X-rays and electrocardiograms (ECGs).
- Characterization and mechanism of action of the drug under development: The regulatory writer should understand the basics of the chemistry, manufacturing, and control of the drug, including the drug substance and the final drug product as well as the pharmacology of the drug, including its pharmacokinetics and pharmacodynamics (that is, what the body does to the drug and what the drug does to the body).
- The indication (that is, disease or condition) under investigation: The regulatory writer should understand the etiology of the targeted condition (eg, asthma, multiple sclerosis, diabetes, obesity, infections caused by Gram-negative or Gram-positive pathogens resistant to current antibiotics), current treatments for the indication, and the immunological response of the body to the drug in healthy individuals and individuals with the proposed condition for treatment.

Linkable documents: As mentioned earlier, the FDA encourages the creation and submission of eCTDs. Therefore, the regulatory writer must ensure that any document created must be linkable to an XML backbone, the technological core of the eCTD. Competencies allowing realization of this standard include: 1) strong knowledge of basic software programs (eg, MS Word , especially the Styles feature, MS PowerPoint, MS Excel, and Adobe Acrobat); 2) ability to create and format tables (in MS Word), figures (in Prism or other graphing software), and study diagrams (in MS Visio or other drawing software); 3) ability to use and maintain templates; and 4) knowledge of how to archive and retrieve documents.

Clearly written, well argued documents: A regulatory writer tells the story of the drug, but more importantly, argues the case for its approval. Competencies that allow this include a command of basic writing skills (eg, organization and logic as well as mastery of syntax, grammar, and punctuation) and knowledge of scientific style, including the in-house style of the sponsor for whom the regulatory writer works.

Strategies for Content Re-use

The CTD contains information and data that are repeated over and over in different contexts throughout the application.

Access to building blocks of content, sometimes referred to as "topics," allows re-use (often called "repurposing") of information and rapid creation of documents that are more often than not written under tight timelines and by multiple authors. Sponsors may create topics by 1) establishing a folder on a common drive with files that contain standardized language and information, 2) approving the content of particular document (eg, the most current clinical study report) for re-use, or 3) implementing sophisticated software that enables direct access to approved "topics," which the writer will modify appropriately for the document under creation. Often, the writer is asked to work with subject matter experts (the clinician, biostatistician, toxicologist) to create the topics in the first place.

Finally, and not altogether incidentally: Getting along with people and being part of a team

A regulatory writer does not work alone. Creation of regulatory-compliant, scientifically accurate, internally consistent documents results from successful teamwork and interaction with others. A writer obtains data and other information from people in all parts of an organization; works with others to craft interpretations of the data (often called "messages"); circulates documents for review; adjudicates comments from colleagues; and finalizes a document for publication into an electronic format. A team review of a document may result in a re-conceptualization of the document; consequently, the writer may have to revise it from the ground up. A successful document depends on the writer's willingness to get along with and learn from others and, when necessary, to subordinate his or her ego or to assert him or herself. If such behavior does not come naturally, many courses sponsored under the loose category of "leadership" and "management" exist that teach people how to work and play together on the job. Interpersonal skills are serious skills, and a lack of them will ruin the career of a regulatory writer.

In addition, the regulatory writer must keep in training. A writer should regularly perform a gap analysis, identifying areas that impede his or her ability to function as a writer (for instance, do you need to learn about Bayesian analyses or the latest FDA guidance about where to place the ISS and the ISE in the CTD?) and have a development plan that enables ways to plug those gaps. The world of drug development is never static, and in this fast-paced environment, a successful writer is one who keeps learning.

Summary and Conclusion

A drug application in eCTD format enables efficient reviews by regulatory agencies, which in turn allow new medicines to be brought to those in need. A regulatory writer participates in this effort by creating scientifically accurate, clearly written, eCTD-compliant documents. The eCTD is here to stay. And so are regulatory writers who can write eCTD-compliant documents.

Resources

Key Regulations and Guidelines

21 Code of Federal Regulations (21 CFR):

- 312: Requirements for an investigational new drug
- 314: Requirements for applications for approval and marketing of a new drug
- 58: Description of good laboratory practices for nonclinical studies associated with clinical trials
- 56: Specifications for institutional review boards that oversee clinical trials
- 50: Specifications for protection of human subjects in clinical trials
- 11: Electronic submissions and signatures

Key ICH guidelines:

- M4: Organisation of the Common Technical Document or the Registration of Pharmaceuticals for Human Use M4. Current Step 4 version dated 13 January 2004
- The Common Technical Document for the Registration Of Pharmaceuticals for Human Use: Quality – M4Q (R1) Quality Overall Summary of Module 2, Module 3, Quality. Current Step 4 version, dated 12 September 2002.
- The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S(R2) Nonclinical Overview and Nonclinical Summaries of Module 2 Organisation Of Module 4. Current Step 4 version dated 20 December 2002.
- The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy – M4E(R1), Clinical Overview and Clinical Summary of Module 2, Module 5 : *Clinical Study Reports, Current Step 4 version dated 12 September 2002.*
- CTD Table of Contents Headings and Hierarchy http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmission

Requirements/Electronic Submissions/UCM163175.pdf .

- E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Current Step 4 version dated 27 October 1994.
- E3: Structure and content of Clinical Study Reports: E3. Current Step 4 version dated 30 November 1995.
- E6 (R1): Guidelines for Good Clinical Practice. Current Step 4 version dated 10 June 1996 (including the Post Step 4 corrections).
- E8: General Considerations for Clinical Trials: E8. Current Step 4 version dated 17 July 1997.

Other Important Guideline/ References:

- US Health Insurance Portability and Accountability Act (HIPAA). (http://www.hipaa.org/), accessed 01 November 2009).
- This Act ensures the privacy of data related to an individual's healthcare.
- CDISC glossary. This is an important source of standard terms: http://www.cdisc.org/glossary.

Style and Formatting Guides

- AMA *Manual of Style,* 10th edition.
- *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publisher*, 7th edition.
- Peter G. Aitken and Maxine M. Okazaki, *MS Word for Medical and Technical Writers.*

Guide to Regulatory Writing

- Linda Fossati Wood and MaryAnn Foote. *Targeted Regulatory Writing Techniques: Clinical Documents for Drugs and Biologics.*

General Reference Books

- *The Merck Manual* (physician and home editions).
- Donald J. Birkett. *Pharmacokinetics Made Easy.*
- Neil M. Davis. *Medical Abbreviations: 28,000 Conveniences at the Expense of Communication and Safety, 13th edition.*
- Frances Talaska Fischbach. *A Manual of Laboratory & Diagnostic Tests.*
- Tom Lang. How to Report Statistics in Medicine, 2nd edition.
- RAPS. Fundamentals of US Regulatory Affairs, 6th edition.
- *Stedman's Medical Dictionary.*
- Linda Skidmore-Roth. *Mosby's 2007 Nursing Drug Reference.*
- Bert Spilker. *Guide to Clinical Trials.*

Magazines and Journals

- *Applied Clinical Trials* (trade journal).
- DIA publications, especially the *Drug Information Journal* and the *Global Forum.* ■

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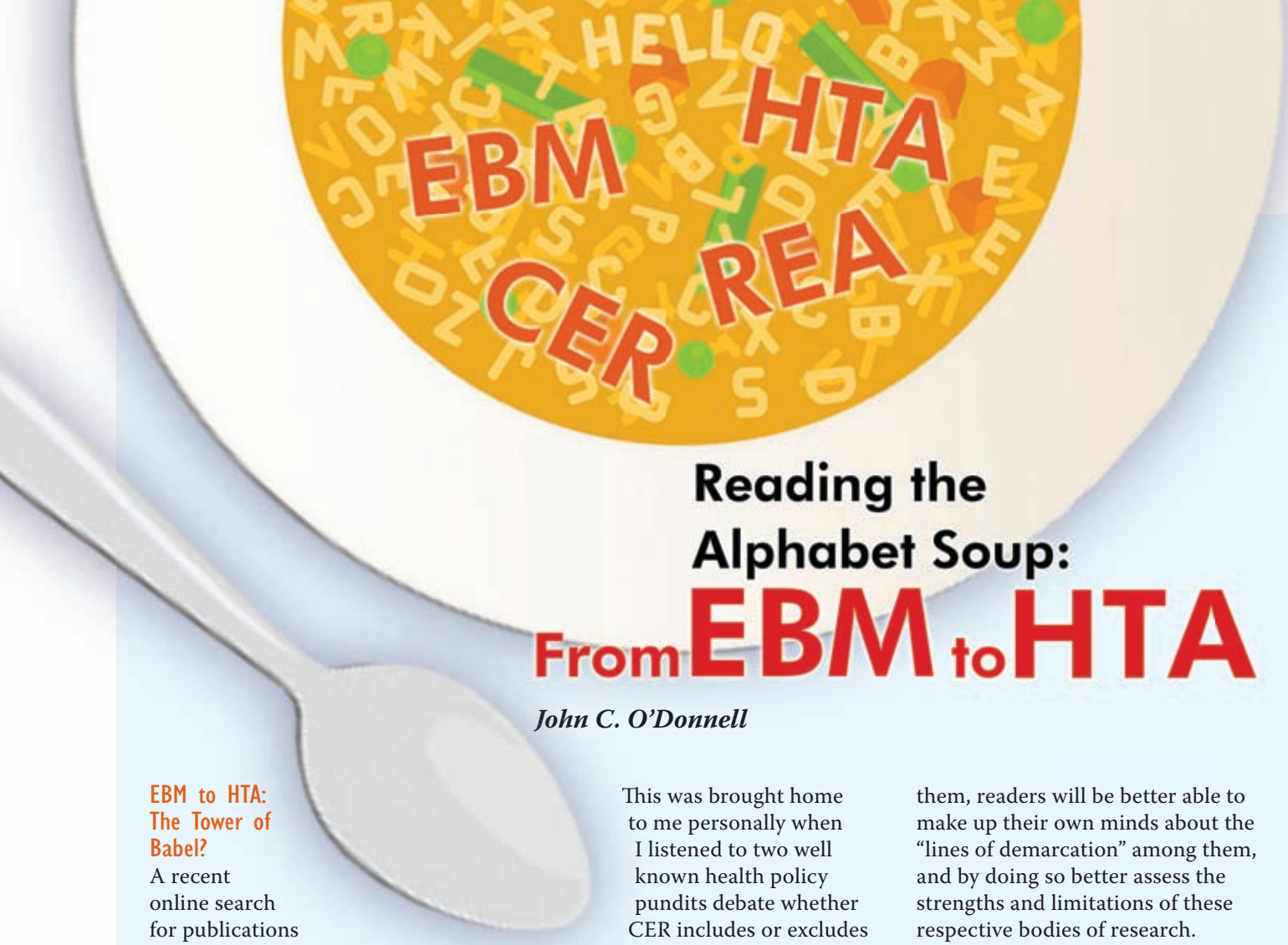
To Learn More, Plan to Attend these Annual Meeting Sessions

- Clinical Study Report Appendices: For Better or Worse (Tuesday, 4:00-5:30 PM)
- Authoring CTD/eCTD Submissions: Experience from FDA and Industry (Wednesday, 1:30-3:00 PM)
- Global Strategies in Medical Writing: A Perspective from Asia (Wednesday, 3:30-5:00 PM)



Reading the Alphabet Soup: From EBM to HTA

John C. O'Donnell

EBM to HTA: The Tower of Babel?

A recent online search for publications addressing "evidence-based medicine, (EBM)" "comparative effectiveness research (CER)," "health technology assessment (HTA)," and "relative effectiveness assessment (REA)" yielded over 2,000 full-text articles, which by any measure reflects an impressive body of inquiry. Beyond this volume of research, what was striking, however, was the variability with which investigators labeled research of a similar type. One could easily find, for example, a systematic review of existing research labeled "CER," while a very similar analysis was dubbed "EBM" or "REA" elsewhere. Similarly, those of us inveterate Congress-watchers who have followed the debate on CER as part of the deliberations on US health care have witnessed time and again confusion about what the terms CER, EBM, HTA, and REA represent, how they are similar, and how they may differ.

This was brought home to me personally when I listened to two well known health policy pundits debate whether CER includes or excludes randomized clinical trials (RCTs). The debate didn't come to blows, but one did get a sense that while some of the confusion about this fundamental distinction was purely a matter of language and syntax, the rest had the feel of an interdisciplinary polemic. Either way it was clear to me that if the policy experts were confused, how could CER stakeholders–patients, providers, and payers–make sense of this area? And how collectively could we plan to deliver a body of research that no one seemed able to fully define? Accordingly, this overview, geared for the novice, seeks to illuminate the commonalities and distinctions among this assessment "alphabet soup." At the end of the day, it is clear that while there will always be some overlap among these concepts – and the corresponding debate will continue – it is hoped that by comparing and contrasting them, readers will be better able to make up their own minds about the "lines of demarcation" among them, and by doing so better assess the strengths and limitations of these respective bodies of research.

Definitions in the "Assessment Alphabet Soup"

How then have these concepts been defined? We begin by offering their definitions as penned by the individuals and organizations that first created the assessment alphabet soup itself. We will then go on to compare and contrast these concepts along a number of salient distinguishing characteristics related to focus, organization, and delivery.

Evidence-based Medicine

Definition: The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. Over time, EBM evolved to distinguish evidence-based individual decision-making (EBID) from evidence-based clinical guidelines, the latter intended to apply to groups of patients rather

than to individual patients as in EBID.[1]

Purpose: To integrate individual clinical expertise with the best available clinical evidence from systematic research to diagnose and treat patients at the individual and population levels.

Distinguishing Characteristics: EBM emphasizes the physician-patient interface in decisions involving diagnosis and treatment. There is a primary reliance on the synthesis of existing data rather than *de novo* data collection. A key goal of EBM is to promote rigorous clinical guidelines. It seeks to move clinical practice toward fact-based decision making and away from the often anecdotal and idiosyncratic practice decisions made historically in medicine. Intrinsic in EBM is the identification and remediation of current gaps in the knowledgebase, though this is typically not a centralized process.

Health Technology Assessment
Definition: A form of policy analysis that examines the consequences of the application of a health care technology. Assessments include safety, efficacy, real-world effectiveness, cost and cost-effectiveness as well as social, legal, ethical, and political implications.[2]

Purpose: To inform health care policy makers about the benefits, risks, costs, and appropriate use of health technology, and any wider impact on a population or society.

Distinguishing Characteristics: Largely "statist" (ie, government sponsored, funded, and staffed) execution with clear and direct links to national clinical guidelines and reimbursement in most countries. HTA explicitly or implicitly includes political, ethical and cost considerations. Heavy emphasis on systematic review, but some *de novo* data generation conducted.

Comparative Effectiveness Research
Definition: The generation and synthesis of evidence that compare the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.[3]

Purpose: To assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

Distinguishing Characteristics: Inherently comparative, describing results at the subgroup level, and measuring benefits in real-world populations. CER places a significant emphasis on physician decision making and *de novo* research activities. It does include RCTs, but tends to emphasize pragmatic trials and real-world performance. CER often does include costs and may be used to assess health care efficiencies, but typically possesses no formal link to reimbursement. The CER nomenclature is decidedly US-based and supported with both government and commercial funding.

Relative Effectiveness Assessment
Definition: The extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.[4]

Purpose: To compare health care interventions in practice in order

	Assessment Type*			
Characteristic	EBM	CER	HTA	REA
Emphasis on physician decision making	+++	++	++	++
Involves *de novo* research activities	+	+++	++	+
Includes H2H randomized clinical trials	+++	++	+++	+++
Emphasis on real-world data	+	+++	++	++
Yields/supports clinical guidelines	+++	+	++	+
Includes cost-effectiveness	–	+	+++	–
Includes link to reimbursement	+	+	+++	++
Uses a formal hierarchy of evidence	++	+	+++	+++
Includes ethical and legal issues	+	+	+++	+
Emphasis on systematic reviews	+++	+	+++	++
Includes mechanisms for priority setting	–	+	+++	++
Largely statist execution/implementation	+	++	+++	+++

*Table 1. Research Assessment Type by Salient Distinguishing Characteristics. *Rating indicates relatively less (+) to more (+++) emphasis on this distinguishing characteristic in this respective assessment type; (–) indicates none or not applicable.*

to classify them according to their practical therapeutic value.

Distinguishing Characteristics: Heavy reliance on systematic review but some *de novo* research activities, including comparative observational designs. Primary focus on clinical benefits and harms; typically excludes cost-effectiveness. The use of this terminology is decidedly EU-based, emanating from a pan-European context and fostered at the European Commission level. It is largely statist in execution, with links to national clinical guidelines. It can include priority setting and may evolve links to the regulatory approval process.

Comparing and Contrasting the Assessment Alphabet Soup

As one can see through even this rather cursory recounting of definitions, there is a considerable level of commonality among these assessment types – even overlap. For example, CER and REA appear to be very similar enterprises, the primary differences being their center of gravity in the US versus the EU, and perhaps the proclivity for REA to be proffered more by governmental authorities, ie, statist in nature, while CER has a rich history in the academic community as well. Table 1 offers a comparison across a range of salient distinguishing characteristics. I intentionally elected to use a "plus-minus" rating scheme because it is clear that many of these distinctions lie along a continuum rather than "yes-no" or "zero-sum" bipolar framework.

Some obvious insights emerge when the assessment types are arrayed in a matrix like this. Most obvious is that while we see overlap in definitions, there is little in the way of lock-step rankings among the types. That is, no one assessment regime appears to be a mirror image of another. Another observation is that HTA appears to be the most comprehensive assessment regime, with three pluses (+++) in eight of the twelve characteristics assessed. This latter point begs the question: How do we see the interdependencies among these assessment types? For example, is one assessment process wholly subsumed in another? Accordingly, Figure 1 offers a heuristic depiction of the interdependencies among EBM, HTA, CER, and REA.

As implied by Figure 1, it seems clear that HTA benefits from the development and application of EBM. Similarly, CER underpins the HTA process; but at the same time CER contributes to both EBM *and* HTA. We might refer to these relationships as "enabling," with the outputs of CER, for example, providing inputs for decision making in EBM and HTA.

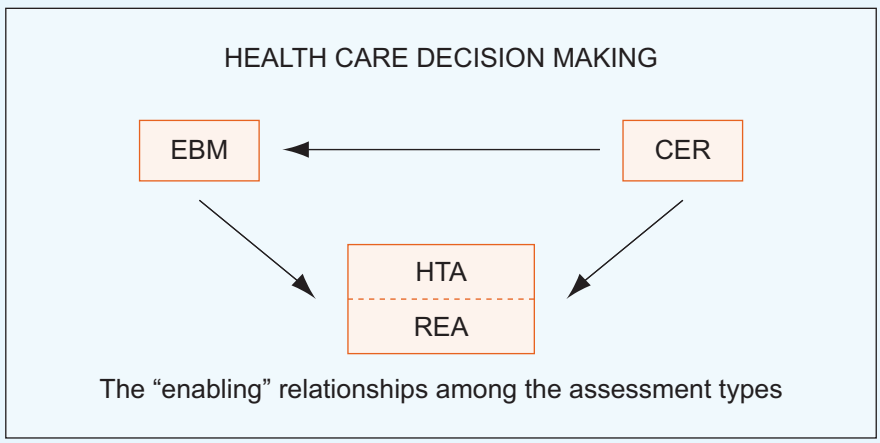


Figure 1. Interdependencies among EBM, HTA, CER, and REA. EBM= evidence-based medicine; HTA = health technology assessment; CER = comparative effectiveness research; REA = relative effectiveness assessment.

While REA by definition sounds very much like CER, one is hard pressed to see it as exogenous to an enterprise like HTA, at least as we have seen REA operationalized in Europe. There, most frequently, the use of the term "REA" refers to the *relative* comparisons of clinical efficacy and safety that underpin the HTA decision-making process – the core clinical assessment that underlies the HTA appraisal itself. Notably, the European Medicines Agency has established a new collaboration with EUnetHTA, a European Commission-sponsored effort to create "core" REAs for Member States' HTA processes, with the expressed goal being to harmonize the many REAs across the EU.

Final Words on the Assessment Alphabet Soup

Few recent issues in health care have generated more commentary than HTA, CER, and REA. The sharp interest stems, of course, from the high stakes involved. For regardless of differences in definition and application, it is clear that HTA, CER, REA, and even EBM, bring together public and private interests in processes in which there are potentially winners and losers, and the perception of outcome is highly contingent on each actor's point of view.[5] In such a high-stakes debate, words – and definitions – matter. The lexicon of health care decision making has reached even the halls of the US Congress and the White House. Political pundits have even quipped about "CER," spelled with capital letters, versus "cer" in lower-case letters, the former presumably referring to a new CER bureaucracy representing so-called big government intervention in health care versus "cer," a legitimate scientific research comparing the benefits and risks of health care interventions.[6] As Senator Max Baucus stated in a recent presentation at a health policy summit, "…Since the Finance Committee began to pray in for a comprehensive health reform last year, comparative

effectiveness research has been mentioned very often. It's almost constantly mentioned, and it has raised almost as much controversy. It's a hot topic, so much so that senators on my committee on both sides of the aisles suggested that we stop using the name, stop calling it 'comparative effectiveness research.' They suggested that we switch to something else that is a little less controversial in its branding.

So we talked about this one day and I, just off the top of my head, said let's call it FRED. That might be more palatable and less ominous...."[7]

While we might not agree with the senator that the critical enterprise of CER should be called "FRED," we are impelled to observe that common ground will be elusive if we cannot at least understand what we are debating. It is indeed time to understand the alphabet soup and get on to the next course.

Notes

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2. Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms. Lawrenceville, NJ: International Society for Pharmacoeconomics & Outcomes Research, 2003. HTAi consumer and patient glossary. A beginner's guide to words used in health technology assessment. HTAi, 2009.
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4. Core principles on relative effectiveness. EC Pharmaceutical Forum Working Group on Relative Effectiveness, 2008.
5. See for example: O'Donnell JC, Pham SV, Pashos CL, et al. Health technology assessment in evidence-based health care reimbursement decisions around the world: an overview. Value Health 2009;12 (Suppl. 2):S1-5.
6. See for example: Who's against Comparative Effectiveness Research? Richard N. Fogoros, MD, http://covertrationingblog.com/comparative-effectiveness research/ who_is_against_ comparative _effectiveness_ research, 2010.
7. Senator Max Baucus. Presentation at Engelberg Center For Health Care Reform and Hamilton Project Event. *Implementing Comparative Effectiveness Research: Priorities, Methods and Impact on Health Care*. Anderson Court Reporting, June 6, 2009. ■

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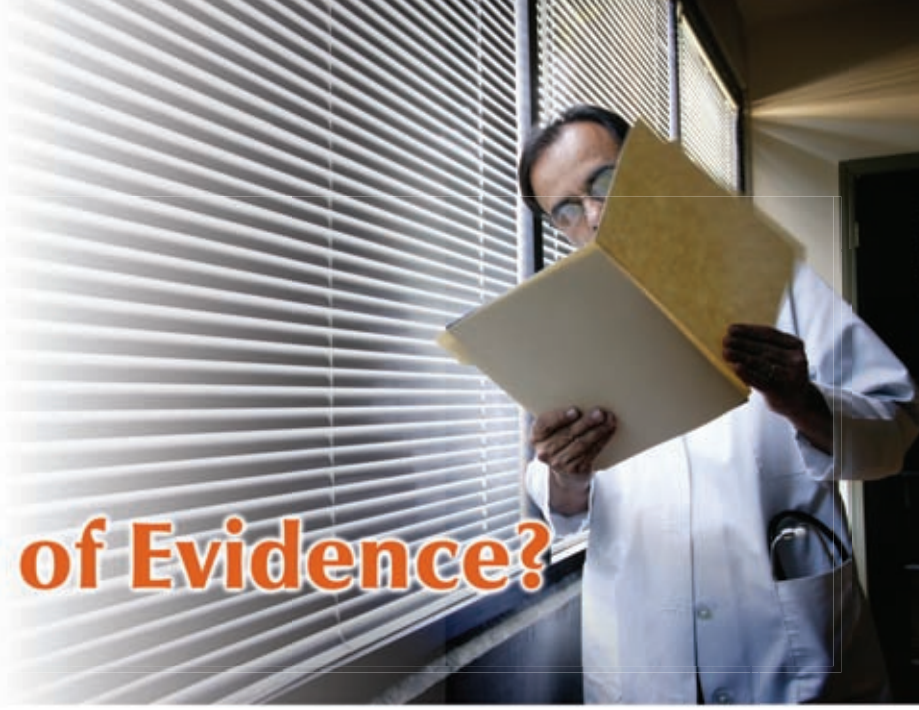
The *Global Forum* would like to thank Dr. C. Daniel Mullins for serving as section editor for the CER/HTA/EBM section.

Dr. Mullins is a Professor within the Pharmaceutical Health Services Research Department at the University of Maryland School of Pharmacy. He received his BS in Economics from M.I.T. and his MA and PhD in Economics from Duke University. His research and teaching focus on pharmacoeconomics, outcomes research, and health disparities research. He is the Principal Investigator of a NIH/NIA sponsored grant on "Response to Medicare Reimbursement Policy Change by Minority and All ESRD Patients" and the lead economist on an NIH/NHLBI grant with Elijah T. Saunders, MD. Section member for the National Cancer Institute (NCI).

He is a co-editor for *Clinical Therapeutics* and *Value in Health* and is author/co-author of over 100 peer-reviewed articles and book chapters.Dr. Mullins was a member of the Maryland Health Care Commission Hospital and Ambulatory Surgical Facility Report Card Steering Committee. In 2002, he was the recipient of an Outstanding Service Award from the Drug Information Association and in 2006 and 2008 he received an International Society For Pharmacoeconomics and Outcomes Research Service Award. In 2007, he received the *Dr. Patricia Sokolove Outstanding Mentor Award* from the University of Maryland, Baltimore campus-wide Graduate Student Association.

C. Daniel Mullins, PhD

Comparative Effectiveness Research: The Evolution of Evidence?



Sandra Leonard and Matthew Rousculp

The essence of comparative effectiveness research, or CER, is the practice of exploring which medical interventions work best for whom, and under what circumstances. This is accomplished by comparing two or more health care interventions, each aimed at the same health outcome goal. When appropriately applied, the information derived from CER can contribute to improving the quality of patient care and to maximizing the value of health care expenditures.

Although CER has recently found its way into news headlines and legislative language, the concepts behind it are not new. In fact, CER appears to be another step in the long quest to support best patient care through medical evidence.

Is CER an evolution of previous evidence-based health care initiatives, or is it a revolution? The initial response is that it is a little of both. The underlying premise of CER, that is comparing medical interventions in real-world settings, is by no means a 21st century notion. The idea of health-related effectiveness comparisons is mentioned in the Bible for comparing differing diets and the effect on perceived health. Other recorded studies from the Song Dynasty in China examined the effect of ginseng on patient's well-being. Many similar examples of comparative evidence dot the history books of medicine.

> *Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" setting. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."*
>
> *Federal Coordinating Council for Comparative Effectiveness Research's Report to the President and the Congress July 30, 2009*

In the 1970s, John Wennberg and colleagues at Dartmouth began documenting the wide variation in medical practice in the different regions of the United States. This was closely followed by the IOM's assertion that only 15% of medicine practiced in the US is truly based on solid clinical evidence. As a result of the compounding knowledge of the discrepancy of medical practice, the following 30+ years has seen an explosion in evidence-based health care initiatives with evidence-based medicine, guidelines, coverage, performance measures, and policymaking. Subsequently, structured processes have evolved such as health technology assessments, Cochrane Collaboration reviews, and the Grades of Recommendation Assessment Development and Evaluation Working Group (GRADE).

At the core of each of these evidence-based initiatives remains the goal of closing the chasm between what is known through clinical research and what is practiced in the community. With this perspective in mind, CER seems to reflect an evolution of providing practical clinical evidence to improve patient care.

However, CER reflects a seismic shift in the generation of evidence as well as its ultimate application.

First, the scope of what constitutes CER has expanded from a primarily systematic approach of assessing existing studies to include the creation of evidence through real-world studies and practical trials. These studies present unique issues for consideration, such as what constitutes effectiveness (eg, clinical endpoints vs. patient reported) and what interventions should be compared (eg, drug vs. drug or device vs. standard of care). Second, in addition to clinicians, payers, and policymakers, the audience for CER has expanded to include the consumers of health care: patients and their caregivers.

Where is the state of CER today?

The recent $1.1 billion allocation from the economic stimulus bill reflects a nearly 100-fold increase in federal funding for CER. In comparison to the $15 million with which AHRQ initiated the Effective Healthcare Program in 2003 as directed in Section 1013 of the Medicare Modernization Act, this investment in evidence is monumental. Although the Federal Coordinating Council on Comparative Effectiveness Research and the IOM reports have helped to guide the federal CER investment dollars and perhaps map the direction of CER, it is unclear how this one-time bolus of funds will impact evidence-based initiatives and ultimately patient care.

While much attention has been spent analyzing the impact of recent CER funding decisions, perhaps the greatest impact on the current state of evidence generation is a result of other funding and regulatory decisions. The vast majority of federal funding for biomedical research has focused almost entirely on preclinical studies. This in addition to regulatory activities such as the Kefauver-Harris (K-H) Amendments of 1962, which greatly improved drug development, may have also inadvertently impeded clinical effectiveness research. The K-H Amendment led to the current phase 1-3 study designs used to ensure regulatory approval and subsequent market access for pharmaceuticals and biologics. This amendment raised the importance of internal validity in studies to measure drug safety and efficacy. Yet, it is argued that the K-H amendment may have inadvertently downplayed the importance of external validity; that is, the effectiveness of interventions in patients who are treated in the community clearly defining what effectiveness means and from whose perspective, is of increasing importance due to the growing role of a key stakeholder: the patient. Quantifying a disease's toll from both the patient and the caregiver's perspective, as well as the significance of an intervention's benefits and the burdensomeness of its harm must be accurately captured in order to clearly illustrate the value of the compared treatment options. Recently, the FDA provided guidance for incorporating patient-reported outcomes as part of the clinical package for drug and device submissions. These efforts, coupled with existing practices for understanding patients' quality of life allow the patient perspective to be included in effectiveness studies.

Are there lessons learned that ensure the promising benefits from CER?

David Eddy, a prominent clinician, is credited with coining the term "evidence based." He provides an insightful history on evidence-based medicine (EBM) in a *Health Affairs* article. He posits that EBM developed along two parallel tracks, one yielded "evidence-based guidelines" and the other as "evidence-based individual [physician] decision making." The guidelines based on evidence are routinely created with multidisciplinary teams using rigorous and time-consuming methods to yield a generic guideline covering most patient groups. Guidelines are intended to inform clinicians and policymakers about existing evidence, but not to provide direct guidance for any one specific patient. For individual decision making, the goal is training the clinician to use evidence-based methods to develop the most appropriate management for a specific patient. Eddy summarizes that the lesson learned is that neither approach is sufficient alone, but that better alignment of these two approaches is vital to ensure the practice of more timely and patient-relevant evidence-based medicine.

The term "comparative effectiveness research," while primarily referenced in the United States, shares the underlying concept of offering pragmatic and actionable research to meet the needs of payers (private or public), patients, clinicians, and policymakers with many other countries. Throughout the world, CER is being used to make population-level health care decisions. In 2004, France's Haute Autorite de Sante, or HAS, initiated an evidence review program similar to other global markets with a stated purpose for evaluating medical effectiveness. HAS has primarily synthesized existing clinical and observational studies, although it is increasingly using economic modeling, public health analyses, and other data sources for analyses. HAS, as well as other similar global organizations including the UK's NICE, Germany's IQWIG, and

Australia's PBAC, utilize several core procedural principles in using CER for real-world decision making. These include the need for CER or HTA entities to be independent, transparent, and inclusive. Timely decision making as well as the ability to contest such decisions have also been identified as vital to the success of such organizations.

Building on the Evidence Base

Regardless of the outcome of health care reform legislation in the US, the desire for more evidence to inform medical decision making and to improve patient outcomes, with the potential for financial savings, will continue to drive comparative effectiveness research generation and utilization. Significant federal funding for health information technology and the greater proliferation of electronic medical records can improve the research communities' ability to ask and answer relevant questions utilizing real-world data.

Continuing along the evidence evolution, the opportunity exists to transcend the chasm from scientific knowledge to realized patient outcomes. Successfully making that leap may require that researchers in academia, clinical practice, public health, industry, and government agencies world-wide approach the pursuit of evidence generation from the perspective of the patient.

How CER will be generated and utilized in the US health care system is still being determined. Will it be another footnote in evidence-based research much like the lauded Office of Technology Assessment? Although the answer is uncertain, it is clear that the need for strong evidence answering relevant clinical questions will continue to be in high demand. Ultimately, the relevance of CER will be determined by its applicability beyond academic publications, to the dialogue between physician and patient.

If successful, the growing evidence base will provide many benefits to patient care, yet it may present some challenges. Without a transparent and inclusive approach in both the generation of effectiveness research as well as its application, the quality of comparative effectiveness reviews will be difficult to assess for patients, providers, policymakers, and payers alike.

References and Notes are available from Matt Rousculp. ■

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To Learn More, Plan to Attend These Annual Meeting Sessions

- Comparative Effectiveness Considerations in Venture Capital Funding Decisions (Monday, 3:30-5:00 PM)
- Implications of CER for Health Care Innovation (Tuesday, 8:00-9:30 AM)
- Comparative Effectiveness Research: Where Is it Headed in the US? (Tuesday, 10:00-11:30 AM)
- Payer Perspectives of Evidence-based Medicine and Comparative Effectiveness: Making Evidence Matter in the Marketplace (Tuesday, 2:00-3:30 PM)

Enhancing Patient Access to Innovative Medicines - European regulators and HTA scientists discuss possible visions for the future

Wills Hughes-Wilson and Angelika Joos

The DIA organized its first Health Technology Assessment (HTA) Forum on 25–26 November 2009 in Paris, France. This first Forum covered a complicated and, for many, a new area by marking a move towards increasing cooperation between two traditionally distinct disciplines of regulatory and HTA. The goal of the meeting was to explore the increasing interaction between regulatory and HTA agencies, and to build understanding of how companies could engage with this process to secure market access beyond Marketing Authorization.

As many companies know, receiving a marketing authorization is, in reality, just the start and not the end of the process of getting a treatment to patients. For many participants at the Forum, the players and processes involved in assessing a new technology and securing reimbursement at the national level – beyond the risk-benefit assessment – are new, unclear, and evolving. Throughout the eight sessions, speakers from all parts of the process led participants at the Forum through the emerging landscape, ranging from definitions and key principles of HTA, through to what can be expected in the future.

That HTA should stimulate, not punish, new technological advances emerged as a strong theme during the two days. The keynote speaker, Paul Gross, Director of the Institute of Health Economics & Technology Assessment, Australia & Greater China, pointed in particular to the emergence of personalized medicine as something that could bring great benefits. He expressed doubts about whether current HTA systems were capable of addressing new, emerging technologies, and speakers from across the panels stressed the need to ensure that good treatments get to patients. This is the ultimate goal of any medicines evaluation system.

What is the Goal of HTA?

The main purpose of HTA is to allow health care decision makers to make informed, data-driven decisions on whether a new technology should be made available in publicly funded healthcare systems, as Anita Burrell (sanofi-aventis) pointed out in her presentation. While methodologies vary between countries, most look at the health benefits and risks of using a technology – as well as, ideally, the costs and any wider impact on a population or society. It is a new, emerging and complex field, exemplified even by the differing definitions currently in use.

Echoing the need to support innovative technologies and treatments for the benefit of the patient, including personalized medicine, Isabel de la Mata of the European Commission argued that, so far, authorities have only considered treatments for entire populations, but that personalized medicine will change the way HTA is carried out. This increases the challenges for HTA systems. While she was clear that reimbursement decisions should remain at the national level, there is a clear added value for scientific evaluations at EU level. Core methodologies can be developed in cooperation, and a pooling of expertise is beneficial to build the best evaluation methods and to avoid duplication.

HTA Cooperation-Now and in the Future

Max von Olenhusen (Novartis European Public Affairs) outlined the legislative proposals for the establishment of a network of national HTA bodies in the EU's draft Cross-Border Healthcare Directive. These foresee the exchange of objective, reliable, timely, transparent, and transferable information on HTA between EU Member States. This is already happening in practice, but the Directive would enshrine a commitment to cooperation in legislation. Finn B. Kristensen, Chair of the EUnetHTA Executive Committee, informed participants that Member States are already cooperating in the EUnetHTA. EUNetHTA aims at building an understanding of the most effective HTA and relative effectiveness processes and exchanging information between Member States. By creating such a platform, countries involved hope to avoid duplication as well as encourage innovation, partly by informing industry what is needed to evaluate new technologies. EUnetHTA will not build a new framework, nor create a single EU HTA report, but build on existing processes by coordinating between agencies and creating a core model for HTA to facilitate common evidence generation. Member States can then take the information for their national decision making. Member States where HTA is relatively new can also use the forum to learn more about effective and efficient approaches. By being up front about what will be expected, EUNetHTA see themselves as a facilitator for emerging technologies and a stimulant for innovation.

Orphan Drugs & Rare Diseases Leading the Way?

Giulia Del Brenna from the European Commission picked up the theme of Member States cooperating in a European forum by highlighting current proposals to speed up access to "orphan drugs," treatments for rare and serious or life-threatening diseases. Enhancing access to orphan drugs is a European Commission priority, and Giulia del Brenna highlighted the involvement of the Member States and the European Medicines Agency (EMA) in the process by cooperating at EU level to develop the data, while retaining decision making at the national level. The establishment of a working party at the Agency to prepare Common Assessment Reports on the clinical added value of orphan drugs is currently under discussion.

Andrea Rappagliosi (GSK) stressed industry's support for the concept because expertise in rare diseases is both scarce and scattered. He highlighted that all other aspects of an orphan drug's assessment are carried out by experts gathered from across the EU at the EMA. The collation of the clinical added value should also be carried out collaboratively, to provide expertise-based reports for the Member States to use. In this way, EU Member States would pool their scarce scientific expertise to assess the clinical added value of orphan drugs and avoid duplication of procedures at national level. An expert working party at the EMA would deliver a scientific opinion on the assessment of a new drug's clinical added value, which could be used by Member States, supporting and speeding up decisions on pricing and reimbursement.

Solange Corriol-Rohou (AstraZeneca) highlighted industry's challenges of working in an environment where regulators and reimbursement authorities operate independently of each other. She demonstrated how the different processes in decision making not only create delays in access to treatments for patients but also create uncertainties for companies developing the drugs: a marketing authorization is no longer a guarantee of market access but is often the beginning of another process entirely. Industry welcomed the increased cooperation and is keen to know what evidence is required by regulators and payers to secure not just marketing authorization but also reimbursement.

The National Institute of Clinical Excellence (NICE) in the UK has established a Scientific Advice Programme in response to this need from industry, said Carole Longson. She gave an overview of the process and called for industry to make the most of these opportunities by being active participants and users of the system.

The View from the Regulators

Stanislav Primožič of the Agency for Medicinal Products & Medical Devices, Slovenia, echoed the general agreement among stakeholders that too many different assessments on the same or different data sets are being carried out and called for HTA to be streamlined. He echoed the concerns of legislators, industry, and patients by saying that there is unequal access to medicine, a redundancy of input into assessment processes, and suboptimal transparency and efficiency. While recognizing that

the transition will be difficult, he believes that these issues need to be addressed and is fully supportive of the current and proposed activities in this field.

The EMA is already taking steps to increase and improve systems to stimulate new technology and science and to speed up access of innovative treatments to patients, said Hans-Georg Eichler (Senior Medical Officer, EMA). Much data is already available from the regulatory process. And, as part of the Agency's continued drive to be more transparent and predictable, more use could be made of this data. Elaborating on the Agency's plans to increase communication with national HTA bodies, he highlighted the planned changes to the European Public Assessment Reports (EPAR) to make them more useful for HTA assessments. These are published at the time of Marketing Authorization, and contain key information on the generated scientific evidence of approved treatments. Currently, they are rather "static" documents, and the Agency is working with national authorities – including HTA bodies and payers – to understand and respond more to their information needs. The EUNetHTA Joint Action will have a key role to play in facilitating this dialogue.

Eric Abadie (CHMP chairman, Afsapps, France) highlighted the fact that although regulatory decision making is guided by quality, safety, and efficacy considerations, regulators usually ask sponsors to evaluate new medicines versus the existing "gold standard" treatment in order to obtain a marketing authorization.

Rakee Modha of Heron Health, and Spiros Vamvakas, Head of Scientific Advice & Orphan Drugs at the European Medicines Agency, highlighted the need for increased understanding and dialogue regarding the acceptability of surrogate endpoints by health technology assessors and the role of surrogates and biomarkers for regulatory decision making.

François Mayer of the Haute Autorité de Santé (France) went further, elaborating on the use of biomarkers in the context of targeted therapies. This creates challenges for both health technology assessors and health care systems: how should a medication and a related new biomarker be assessed, and will the necessary diagnostic test always be available at the same time? More dialogue is needed to establish how the emerging field of personalized or targeted therapies can be used efficiently for patient benefit.

Jens Grueger (Pfizer) called for companies to assume their responsibility. He stated that companies need to align their internal structure to make use of opportunities for regulatory and payer input into their clinical development. The positioning of a new product and the clinical evidence that is required when developing a new product need to be brought into the process as early as possible to satisfy requirements for both regulators and payers at a later stage. He acknowledged that it is never too early to have discussions with payers and regulators, and that more work needs to be done to enhance this relationship. Jim Furniss of Bridgehead International illustrated this conclusion with a concrete case study.

Are We Capturing the Right Values?

Even with enhanced cooperation, the right tools need to be in place to evaluate the right things, said Steve Bates (Genzyme). He moved the discussion to the considerations included in health technology assessments themselves, which tend to be limited in their focus. He suggested that HTA assessments should take into account the wider impact of a treatment for both the patient and society, giving examples of challenges faced in the UK's HTA process. Iñaki Gutiérrez-Ibarluzea of the Basque Office for Health Technology Assessment, Spain, also explored how the additional value of a new treatment should be assessed. Key questions are: Who determines the value of a treatment? Does the perceived value change, depending on who is making the assessment? Mandy Ryan of the University of Aberdeen looked at the consequences of using narrow criteria for HTA and stressed the important role of patients for a truly comprehensive HTA. The recent "Kennedy review" in the UK has raised some of these questions and concerns around methodologies, and there are moves underway at NICE to address limitations identified with the current approach.

Lesley Greene, a patient representative from Eurordis, picked up the discussion on the necessity of the patient view in any HTA process. Patients are willing to accept decisions of payers, she said, as long as the way in which those decisions are made is clear and transparent. It is also important that the patient view is taken into account in any

decision-making process, as they are the people who will benefit from the treatments being assessed.

What Next?

Isabelle Stoeckert (Bayer Schering Pharma) reiterated the delays that are currently faced by companies in getting a treatment to market after receiving a marketing authorization. She stressed the need to avoid the current duplication of assessments for the same product.

Paul Gross concluded the DIA HTA Forum by stressing that cooperation between all stakeholders is key to reaching the overall goal of improving access to treatment for patients. Consultation alone is not enough, as – in some cases – the wrong questions are being asked. What is required is an increased understanding of what the regulators and payers are looking for when they make their decisions.

It is clear from this Forum that all stakeholders are keen to work together to reduce delays in getting treatments to patients, and that steps are already being taken to make this a reality. Only by continuing such discussions, involving all stakeholders involved in the process, can we really understand what is required to address the challenges. DIA's open and collaborative approach, broad membership, and strong reputation allow it to provide the platform to continue these open discussions, advance the debate, and move a step closer to more effective and efficient HTA in the European Union.

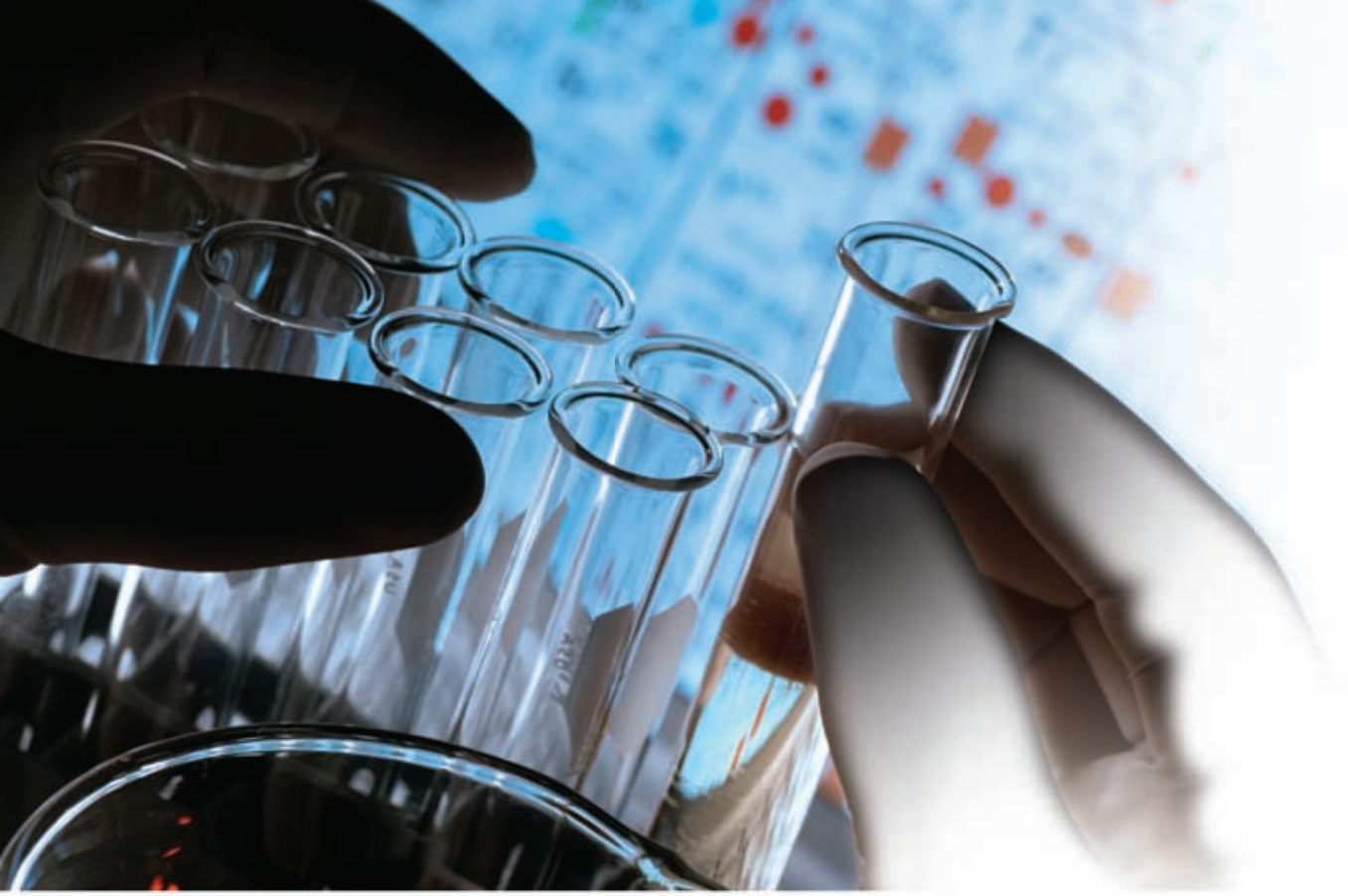
The DIA HTA Forum 2010 is currently being developed, and further details will soon be available on the DIA website: www.diahome.org or from the programme co-chairs. ■

***Wills Hughes-Wilson**, Senior Director, Health Policy Europe, Genzyme, Belgium.*

***Angelika Joos**, Director, Regulatory Policy Europe, Merck Sharp & Dohme (Europe) Inc., Belgium, served as program chairs for the 2009 DIA HTA Forum.*

To Learn More, Attend this Annual Meeting Session

FDA and European Medicines Agency Update on Relative Efficacy/Effectiveness (Monday, 3:30-5:00 PM)



The National Comprehensive Cancer Network's Role in Comparative Effectiveness Research

Edward C. Li and William T. McGivney

Comparative effectiveness research (CER) in the oncology realm exhibits unique challenges as compared to other disease states. Various issues such as the challenges of recruiting patients with cancer into clinical trials and rapidity of knowledge advancement make the use of randomized clinical trials less practical for carrying out oncology CER in some situations. Additionally, the abundance of tumor types, decision nodes within tumor types, patient subpopulations, and genetic differences further highlight the difficulties in conducting oncology CER. These difficulties are factors that lead to an inadequate amount of information related to comparing the outcomes of different health technologies in oncology. It is established that these "information gaps" contribute to variation in care and disparities in health outcomes.[1]

The medical scientific community should actively seek to address these information gaps by utilizing multiple types of CER methods and paradigms in order to ultimately decrease these variations and improve the outcomes of the patients whom we serve. The National Comprehensive Cancer Network (NCCN), being dedicated to this mission, sees an opportunity to become a leader in oncology CER. While CER has become an important topic in the overall context of health care reform, it is important to note that this is not a new concept. In the medical literature, there exist comparisons of different interventions in the form of randomized controlled trials, meta-analyses, and database analyses. Furthermore, when such explicit comparisons are unavailable, clinicians have a long history of formulating comparative effectiveness

judgments by interpreting existing data (for example, resulting in formulary decisions). Much of the recent CER discussion has focused on developing priority topics, proper methods for the conduct of CER, and on how CER results would be utilized to inform coverage policy decisions. Alternatively, NCCN seeks to focus on how oncology CER is collected, interpreted, translated, and disseminated. Since NCCN's primary goal is to improve the quality, effectiveness, and efficiency of cancer care so that patients with cancer can live better lives, it is imperative that NCCN become an active leader in oncology CER. NCCN's role in comparative effectiveness research is in five main areas: 1) identifying priority research areas; 2) maintaining and building data infrastructure; 3) conducting clinical comparative effectiveness research; 4) integrating valid comparative effectiveness analyses into the NCCN Guideline process; and 5) translating and disseminating comparative effectiveness research results.

Identifying Priority Research Areas

As recognized by The Friends of Cancer Research White Paper, it is important to develop a "high-priority, clinically important" research agenda of topics.[2] This research agenda should support the development of personalized medicine through the analysis of subpopulations or clinical biomarkers and should focus on interventions other than treatment such as screening, diagnosis, and end-of-life care. Keeping these factors in mind, the formation of specific hypotheses for oncology CER studies requires expertise from multidisciplinary clinicians (ie, medical, radiation, and surgical oncologists) who deal with these challenges on a daily basis when caring for their patients. NCCN is able to supply this expertise, as the evidence-based NCCN Clinical Practice Guidelines™ are developed and updated by 44 individual panels, composed of over 800 multidisciplinary clinicians and oncology researchers from the 21 NCCN Member Institutions geographically dispersed across the country. Panel members possess in-depth knowledge of the biomedical literature and awareness of, if not actual leadership and/or participation in, the trials that provide the evidence for the NCCN Clinical Practice Guidelines™. During guideline panel deliberations, NCCN clinical experts identify areas for future research.

Maintaining and Building Data Infrastructure

According to the Federal Coordinating Council for Comparative Effectiveness Research, one primary investment area is the development of data infrastructure to allow for the conduct of CER based on secondary data sources (ie, databases).[3] Although it is emphasized by the Friends of Cancer Research that the randomized clinical trial is the gold standard for conducting CER, the analysis of secondary data sources can and will play an important role. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recognized the value of data from retrospective databases and has developed guidance as to good research practices for designing a study utilizing secondary data sources and for analytic techniques that can infer causality.[4,5,6] Specific to cancer, NCCN has created and maintains databases for quality assessment and outcomes research purposes in a variety of cancer types. The NCCN Oncology Outcomes Database™ is a network-based data collection, reporting, and analytic system that describes the patterns and outcomes of care delivered in the management of patients with cancer. The first database was for breast cancer and was initiated in July of 1997. Presently, the NCCN Oncology Outcomes Database™ has five active database components: breast, colon/rectal, non-Hodgkin's lymphomas, non-small cell lung, and ovarian cancers. The database follows more than 60,000 patients with approximately 300 data elements collected on each patient in areas of sociodemographics, clinical interventions, and clinical and nonclinical outcomes. The data is high quality and research-worthy as onsite audits of data occur within three months of a site joining the database and on an annual basis thereafter. NCCN is dedicated to maintaining the current infrastructure and expanding the database into other tumor types. Additionally, future opportunities could compare NCCN data to other databases, for example with SEER-Medicare such that more diverse comparative effectiveness analyses can be conducted.

Conducting Clinical Comparative Effectiveness Research

One current use of the NCCN Oncology Outcomes Database™ is for quality improvement purposes, wherein recommendations and quality measures derived from the NCCN Clinical Practice Guidelines™ are analyzed for the purpose of improving practice performance. The database also serves to identify factors that result in variations of care and is a unique resource and repository of data for researchers to access and derive hypothesis-generating research. With its current capacities, the NCCN Outcomes Database™ is able to perform comparative effectiveness research, and has already started to generate such data. For example, one such analysis in younger patients with Mantle Cell Lymphoma compared the outcomes of R-CHOP alone, R-CHOP plus high-dose

chemotherapy followed by autologous stem cell rescue, and R-HyperCVAD. Results were presented at the 2009 American Society of Hematology Annual Meeting.[7]

Integrating Valid Comparative Effectiveness Analyses into the NCCN Guideline Process and Translating and Disseminating CER Results

NCCN's hallmark role in CER is to translate the results of comparative effectiveness research studies into practical, clinical recommendations and to disseminate this information. The NCCN Clinical Practice Guidelines™ serve as the perfect vector for this purpose, as they are widely recognized and applied as the standard for clinical cancer care in the United States. The NCCN Guidelines and the NCCN Drugs & Biologics Compendium™ are also recognized and used by the Medicare program and by private payers to set coverage policy. The evidence-based guideline recommendations are a translation of the scientific literature into practical clinical recommendations. CER results are part of the evidence used to inform these clinical recommendations.

In 2008, NCCN started the process of developing more concrete recommendations regarding the comparative effectiveness of different treatment options. In version 1.2009 of the Breast Cancer guidelines, the panel stratified adjuvant chemotherapy regimens into "preferred" and "other" categories, noting that this would be followed with a more "comprehensive, systematic evaluation of comparative effectiveness." At the end of 2009, NCCN proposed developing the NCCN Clinical Therapeutic Index (CTI), a paradigm for near-term comparative effectiveness analyses of existing data in oncology. The CTI establishes a framework wherein the expert judgments made by NCCN panel members regarding the effectiveness and toxicity of different treatment options are scored and compared. In judging the effectiveness of various treatments, the panel would consider parameters such as the probability of achieving a cure and the impact on survival, disease control, performance status, and symptom control. Similarly, toxicity judgments would consider parameters such as the probability of death and severe toxicities, the duration of toxicity, the degree of debilitation, and the impact on quality of life. The end result would be a comparison of the effectiveness and toxicity scores of various treatment options displayed in a graph format.

This draft paradigm was released for public comment and presented at the NCCN Oncology Comparative Effectiveness Research Policy Summit on December 7, 2009 in Washington, DC. The policy summit brought together multiple stakeholder groups, such as patient advocacy groups, physicians, insurers, employers, biopharmaceutical companies, and government organizations. There was lively discussion and debate about the CTI and how NCCN should proceed with the process. Currently, NCCN is developing the methodology for scoring and validating the CTI, and anticipates piloting the program in 2011. It is expected that the final CTI process will help to inform clinical decision making and improve the outcomes of patients by translating evidence reports into concrete clinical recommendations.

Summary

The recent dedication of resources towards improving CER infrastructure, knowledge, and dissemination has the potential to improve patient outcomes and enhance efficiency of care. The NCCN recognizes the importance of CER activities, and is developing CER programs specific to oncology. The clinical and scientific experts that serve on NCCN guideline panels are well positioned to identify research priority topics in oncology. Further, the NCCN Oncology Outcomes Database™ serves as an important piece of data infrastructure through which comparative effectiveness research can be conducted. Additionally, NCCN's proposed new paradigm, the "NCCN Comparative Therapeutic Index," will utilize existing data and expert clinical judgment to make more explicit recommendations regarding the comparative effectiveness of different interventions in oncology. This translation of CER studies into practical clinical recommendations would be disseminated through the widely used NCCN Clinical Practice Guidelines in Oncology™. Through these initiatives, NCCN believes it can play a major role in how CER data is generated, translated, and disseminated for the goal of improving outcomes of patients with cancer.

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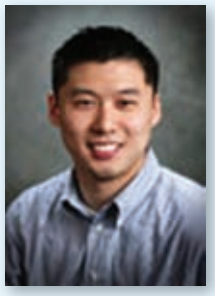

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Can We Get to Personalized Medicine from Comparative Effectiveness Research?

Clifford Goodman

Two high-profile issues that could have been on a collision course are starting to exert mutually favorable influence. One, comparative effectiveness research (CER), is intended to determine which among alternative health care interventions yields better patient outcomes in real-world settings. The other, personalized medicine (PM), is intended to ensure that health care delivers the "right treatment at the right dose to the right patient at the right time."

CER is a recent arrival in health care evaluation that borrows attributes from earlier and ongoing forms of technology evaluation, starting with the first modern randomized controlled trials more than 60 years ago, that usually emphasized a population-based inquiry. CER's current place at center stage coincides with the emerging potential for serving individual health needs that arise from the sequencing of the human genome. Clearly, proponents of PM clinicians, patients, industry, and others do not welcome the prospect that CER might serve to homogenize PM and mask individual and small group differences in response to care.

PM refers to the use of information about individuals' personal traits to better manage their disease or disease risk. These traits include one's genome, health state, personal and family history, and behavioral, environmental, socioeconomic, cultural, and other personal determinants of the impact of health interventions. In some respects, physicians always have sought to practice PM by treating one patient at a time, with more or less consideration for such traits. Drug regimens have been tailored to individual patients' biomarkers, such as weight, blood pressure, and lipid levels. But for the most part, physicians' tools have been constrained, as has their ability to account for more of these personal factors that might affect management of their health care problems. Boosted by the sequencing of the human genome and continued advances in molecular biology, an important emerging tool for PM is pharmacogenomics, the study of how individual genetic differences affect drug response. Adding to the interest in PM at the molecular level is the growing appreciation of the importance of capturing and making use of evidence of patient response among priority populations (elderly, women, children, others), including those that remain underserved in the US.

Contrasting Orientations?

Like other forms of health care evaluation, CER generally has focused on identifying interventions that are effective, on average, across patient populations with particular diseases or conditions. However, interventions that yield a statistically significant treatment effect across a study population may not work for all treated patients; they may be ineffective for some patients and only harmful for others. Other interventions that do not yield a statistically significant treatment effect across a study population—and that may be dismissed as ineffective—may work for certain subsets of that population. If CER does not capture evidence of the differences in benefits and harms experienced by various subgroups, also known as heterogeneity of treatment effects (HTEs), it could

be suboptimal for patient care. This could be the case, especially if CER findings are used to inform gatekeeping functions such as product labeling, clinical practice guidelines, coverage policies, and quality measures. To the extent that CER does incorporate this analytical focus—particularly in prospective study designs—the resulting evidence will be more relevant and useful for these same functions.

The ability of CER to inform health care decisions for specific individuals depends not only on how well the study population represents those individuals; it also depends on whether the study designs and analytical methods used are capable of detecting important treatment effects and adverse outcomes for the patient subgroups representing those individuals. To date, only a small proportion of published comparative effectiveness studies have focused on treatment effectiveness in patient subgroups. By emphasizing research priorities and study designs that capture evidence on HTEs, CER can augment the evidence base to better inform PM.

Rigorous Evidence Requirements Still Apply

The interventions used in PM are subject to generally greater and more specific prevailing requirements for rigorous evidence demonstrating how well they work. In general, this entails evidence from prospective, experimental studies that are designed to minimize the opportunity for bias or inferential error to affect results regarding the true impacts of interventions. Increasingly, this also means showing that an intervention has some direct, or least demonstrably indirect, favorable impact on patient outcomes compared to standard care in real-world practice. For genetic and genomic testing and other diagnostics used in PM, this extends beyond demonstrating technical accuracy of a test. It addresses evidence for analytic validity: the test's ability to measure accurately and reliably a genotype or other analyte of interest; clinical validity: the test's ability to detect or predict the associated disease or condition (phenotype); and clinical validity: the test's ability to affect clinical decisions and patient outcomes in practice.

Methods Portfolio

CER offers an evolving portfolio of methods with great potential for meeting the needs of PM. These methods are being augmented by the CER methods development being supported by the US Agency for Healthcare Research and Quality (AHRQ) and ongoing work sponsored by government and industry on, for example, more powerful and discerning analyses of health insurance claims and other data sources, including clinical registries, electronic health records (EHRs), and socioeconomic data. This also involves efforts to link these sources to discern relationships among patient characteristics, health interventions, practice settings and providers, and outcomes that may provide insights for PM. Of course, appraisal of resulting findings must remain cognizant of limitations of using observational data to explain the impact of interventions on outcomes, though advanced forms of risk adjustment and other statistical techniques can mitigate some of these limitations. Adaptive clinical trials designs and other variations of clinical trials that focus on deriving evidence efficiently for differently responsive patient subgroups offer particular promise for PM.

Innovation

CER offers opportunities for innovation in PM, along with inevitable shakeouts. The need to generate comparative evidence at more discrete levels raises the stakes for innovation and forces choices about its direction and sequence. Technologies that achieve prevailing evidence requirements and demonstrate comparative effectiveness at lower cost or superior effectiveness at acceptable costs will gain market advantages. Federal support for CER and related methods development, data sources, and infrastructure could reduce development costs and boost innovation. For example, analyses of linked databases may help to identify new genetic determinants of drug response and related biomarkers.

Communicating Findings

As CER further accounts for HTEs, the communication and use of these findings must be more adaptive and targeted to clinicians, patients, payers, and the public accordingly. These messages should address any limitations of this evidence for decision making and current evidence gaps that are priorities for further CER. The strengths and limitations of CER and other evidence, including whether it accounts for HTEs as opposed to an average effect across a population, must be accurately reflected in product labeling, guidelines, payment policies, and other gatekeeping policies. To enable evidence-based PM, these gatekeeping policies must

be flexible, adaptive, and updated as new evidence emerges. By supplying valid evidence on subgroup responses, CER can enrich and diversify practice guidelines with more patient-specific pathways. In turn, experts responsible for developing and updating guidelines can translate their observations about pathways lacking adequate evidence into new priority questions for CER.

Role of Health IT

Health information technology (IT) can enable CER and PM alignment. Through capture of genetic and other individual health information in clinical trials and EHRs in clinical practice, health IT can augment the data for CER. Advances in computing power and software are enabling linking, probing, and analyses of large data sets in ways that will yield previously unattainable information on comparative effectiveness at subgroup levels. Health IT must continue to evolve to maintain secure management and exchange of protected health information and personal identification information in computing and analytical environments of linked data sources. Clinical decision support systems and other forms of health IT can ensure that evidence derived from CER and other sources pertaining to PM is present and actionable at the point of decision making by patients and clinicians. The ability of CER to contribute to PM on any systematic and ongoing basis depends on broad adoption of health IT, which has been slow to date, although this will benefit from the infusion of funding from The Health Information Technology for Economic and Clinical Health (HITECH) provisions of The American Recovery and Reinvestment Act of 2009 (ARRA), the law that provided the unprecedented $1.1 billion bolus for CER.

Encouraging Signs

There are encouraging signs for alignment of CER and PM. The definitions of CER in the 2009 reports on CER priorities for the US by the Institute of Medicine (IOM) and Federal Coordinating Council for Comparative Effectiveness Research (FCCCER) acknowledge aspects of PM. The IOM definition cites the need for CER to describe results at the subgroup level; the FCCCER's addresses evidence for diverse patient populations and subgroups in different settings. Among its top priorities, the IOM calls for CER of genetic and biomarker testing and usual care in preventing and treating five major types of cancer and other clinical conditions. The FCCCER calls specifically for PM and CER to complement each other.

Pending health reform legislation in the US Congress calls for CER that accounts for potential differences in effectiveness of interventions as used with various populations, eg, by racial and ethnic group, age group, women, different comorbidities, genetic and molecular subtypes, and quality-of-life preferences. The pending legislation also calls for dissemination of research findings in ways that present considerations specific to certain subpopulations, comorbidities, or risk factors, as appropriate. The initial stream of CER grants and contracts from AHRQ, the National Institutes of Health, and Secretary of Health and Human Services includes aspects of PM. Nevertheless, much work is needed to ensure that these intentions and early signs will actually lead to evidence-based PM.

Summary

The signals approaching the intersection of CER and PM are clear. Population-based evidence must be complemented by personalized evidence about how patients' genetic, genomic, and other personal traits affect their responses to health care, in sometimes unanticipated ways. At the same time, genomic testing and other interventions used in PM have to meet the higher, more specific evidence hurdles that increasingly apply to health technologies. CER priorities, specification of research questions, design and conduct of data collection and analysis, reporting of results, and translation of findings into practice and policy that support PM should be fully integrated. Realizing the benefits of CER and PM on a broad scale depends on wider adoption of health IT. This progress can achieve alignment, and even synergy, of CER and PM to inform delivery of that "right treatment at the right dose to the right patient at the right time." ■

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Comparative Effectiveness Is Essential for Value-Based Design… and VBD is essential for CER

Cyndy Nayer

As the United States considers the priorities and expense of health care insurance reform, many question the consequences of the discussion. If more Americans could be assured of health care coverage, would this guarantee improved health status? The answer to this is, "probably not," since many folks who have health coverage are not engaged in their personal health management. Further, as we concentrate on affordability of insurance, we are simultaneously complicating the discussions with calls for comparative effectiveness of interventions. Yet there is more to consider, particularly with regard to engaging patients in managing their health for the long term.While many have attempted to promote engagement, no one answer works; there are multiple pieces to the "engagement puzzle," and people do not fit nicely into one engagement method or another. People tend to make choices on managing their health based upon multiple answers to the question: What is important to me now?

The bad news is that health interventions only work if the targeted patients who are affected actually "take" or "do" the prescribed intervention—another piece of the engagement puzzle. Hence, the imperative is really to expand the definition of comparative effectiveness research (CER) so that it includes engagement of the personal, clinical, and interventional contributors. In other words, let's be sure we are defining CER to include the engagement of the key players and alignment around outcomes. The best tool for driving outcomes has been the Value-Based Design (VBD), sometimes called the Value-Based Insurance Design (VBID). This article is written to show the connection between CER and VBD and the exponential increase in health status that is possible when the two are considered together.

CER is defined by the Institute of Medicine (IOM] as "the generation of synthesis and evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improved the delivery of care."[1] But what is striking is the next sentence: "The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at the both the individual and population health levels."

With this sentence the link from CER to VBD is made. Value-Based Design is an engagement tool that links the patient/consumer to the plan sponsor to the clinician in order to drive better health and economic outcomes.[2] It is important to note that VBD or VBID is not just about the insurance plan design; it is also the incentive/disincentive structure that influences behavior change in each member of the health value chain, such as the physician/clinician, health plan, pharmacist, employer, consumer, or manufacturer. All of these "sectors" contribute to the health value chain, and they must all be aligned in order to drive the most value from the dollar spent. These insurance plan designs and incentives have been catalogued by the Center for Health Value Innovation (a nonprofit organization disseminating the evidence of the effect of VBD) whose tag line is "the information exchange for value-based design." The business evidence accumulated over 20 years of analysis and data sharing has developed into a dynamic body of learning and maturation through the Center, which reflects domains of levers, or incentives, disincentives, and plan design that influence behavior change:

1. Levers that promote personal health management, usually regarding prevention and wellness (such as reduction in out-of-pocket expense for annual physicals, screenings, or even use of the Personal Health Record);

2. Levers that promote chronic care management (such as reduction in out-of-pocket expense for Rx interventions or incentives for enrolling in condition management programs); and

3. Levers that promote appropriate utilization of care delivery sites (such as reduced co-pay for onsite services or medical travel, or increased out of pocket expense for use of emergency rooms when the condition is not an emergency, or increased payment to the clinician for practicing to the evidence-based guidelines).

Early VBD pioneers reduced out-of-pocket expenses for desirable behavior change in the patient/consumer. The early work at Pitney Bowes by former corporate medical director Jack Mahoney MD showed creating access and affordability for behavioral health and EAP counseling drove improved clinical, Rx, and economic outcomes for the company. Later work from Dr. Mahoney at Pitney showed the increased adherence to asthma, diabetes, and hypertension regimens was more successful when all of the pharmaceutical interventions were reduced to the same formulary tier (tier 1 with 10% co-insurance and a maximum out-of-pocket expense of $20.); there was no mandatory activity needed to receive this savings.The work of John Miall and team in Asheville, NC, linked decreased cost-share for Rx and medical care when the diabetic patient enrolled in counseling with pharmacists and diabetes educators, —and this was a very different model that required participation in education and behaviors (be compliant with the medication and the labs/clinician visits) in order to receive the reduced fees for all services. But the newer models of VBD have linked improved reimbursement to clinicians who improve process and/or outcomes measures, and they have focused on "activity-based incentives" such as incentives for consumers who manage their health-wealth-performance outcomes (such as setting goals and measuring these on their PHRs). [3]

CER can be considered the molecule-to-molecule evidence of effectiveness, but the business community of human resource directors, CFOs, and VPs of Benefits-Compensation would argue that there is just as much need for the effectiveness of engagement strategies and time-to-dividends, such as which plan design plus intervention will lower absenteeism or safety incidences.

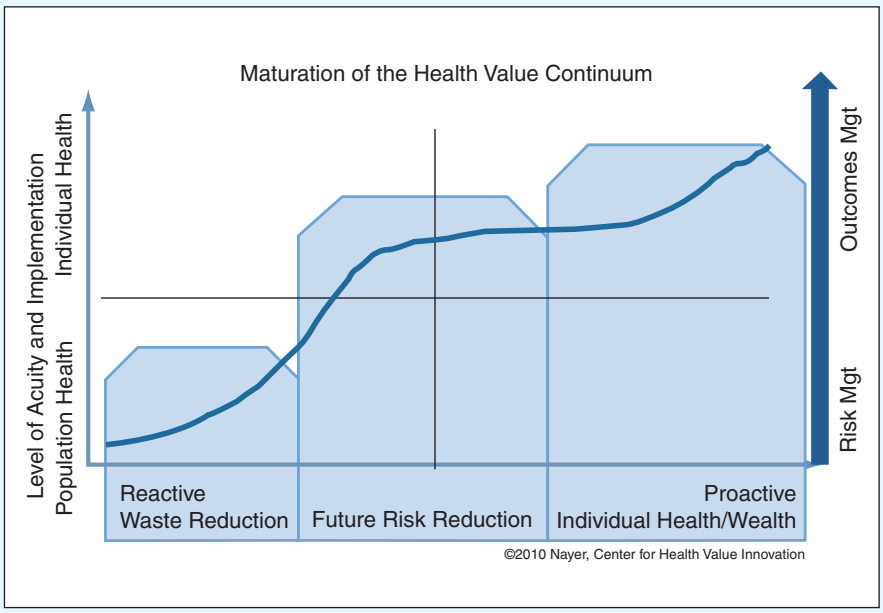

Figure 1

CER IS LINKED TO VBD

By definition, CER is linked to VBD through the highlighted purpose in the opening paragraph of this article: "The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at the both the individual and population health levels." VBD supports effective decisions in plan design, linking the plan sponsor (health insurance plan or self-insured employer) with the consumer and the clinician. It is, therefore, incredibly important to refocus some of the effort of CER within the drug development community to understanding the engagement, challenges, and potential outcomes from each intervention.

Perhaps the best way to understand the connection is to consider the Health Value Continuum, a construct developed within the Center for Health Value Innovation that shows the trajectory and acuity of focus of the plan design (Figure 1).

This continuum shows that organizations move plan design along the *x*-axis from reactive, waste reduction (reducing extraneous costs due to over use, under use and misuse), through future risk reduction (engaging the high-risk population and their providers in efficient and efficacious chronic care management) and into a proactive plan design that creates aligned incentives for better outcomes for each individual. The organizations move plan design along the *y*-axis

GLOBAL FORUM

from a broad-based population health focus to an acuity-based individual health focus, identifying segments of populations that need additional help or nudges to become compliant and persistent in their health management. As each new lever, nudge, or plan design is put into place, some of the population will develop new challenges or not engage—hence the third axis. The *z*-axis is the summary of the movement: plan sponsors move from risk management to outcomes management as new risks develop and new risks emerge that must be managed.

This is the very essence of the CER purpose: to use the business-based evidence and marry it to the clinical effectiveness evidence so that policy (plan design) decisions can be married to engagement tactics, driving sticky behavior change (adherence and persistence).

Outcomes-based Contracting Can Accelerate the Business Evidence of CER

Because clinical phase 3 trials track the adherence and persistence of populations to the studied intervention, CER can be developed that enhances the business-based evidence of engagement.

Plan designers within the VBD community do not analyze engagement or adherence across whole populations. Rather, they analyze data by gender, age, socioeconomic status, and education, among other attributes, in order to create the acutely focused plan design that will engage the member in a meaningful, actionable behavior change. As an example, a plan designer may discover that the overall persistency to a glucose-monitoring drug is 85%, but that men ages 40-55 are not as compliant as women of the same age. Then, a lever can be deployed that nudges the men to engage in condition management as a requisite for reduced out-of-pocket expense for the drug. If one of the analyses for CER were an adherence segmentation analysis, there would not be the time-lapse till the plan designer or the plan sponsor discovered this artifact; it could be part of a total design recommendation with levers that encourage educational enrollment, and, perhaps, physician-driven messaging with more frequency to the at-risk population (men, ages 45-55).

This focus on the outcomes of the intervention, which not only includes "getting to goal" but also promotes the segmentation and messaging necessary to keep more vulnerable patients on the drug, is the essence of an outcomes-based contract. Aligning talent across the touch-points that, together, accelerate adoption, adherence, and persistence is the very essence of improved outcomes that America's businesses need, whether large or small, private or non-profit or government-as-employer.

CER RISK	LINKING CER to VBD Identifying populations-at-risk by severity and aligning levers to outcomes (using diabetes as an example)			BENEFIT LEVER SUGGESTED
Ranking on level 1-10	7	3	5	
Vlunerable population	Males 45-55 less likely to engage CER = 3	Women ages 45-55 at 12 months	Women ages 25-35	Mandatory condition mgt program with reduction in co-pay for the drug offered 2 months before the identified risk begins
Business Measure of CER	Waste: Non-compliance	Future Risk: Non-adherence	Individual Health Mgt: Non-persistence for 2 years	
	Outcomes Desired: Compliance/persistence to treatment and reduced HbA1C Fewer ER and Inpatient Days			©Nayer, Center for Health Value Innovation 2010

Figure 2

Construct for Leveraging Health by Linking CER to VBD

A construct for linking CER to VBD would foster a new dialogue for the pharmaceutical industry with their largest and smallest purchasers. If CER would be used to show the purchaser what populations may not be as willing to adopt the new therapy or less inclined to stay on it, this would cut the trial-and-error timing and change the purchasing from commoditized unit-cost pricing to productized outcomes-based contracting in which gain-share would be a part of the formula. Figure 2 shows an example of how this could work.

Focus on Outcomes Drives Value and Links to Comparative Effectiveness

Often the words that we use when we define the outcomes we desire limit the range of possibilities and solutions. As the CER movement has progressed, it has appeared to focus on the head-to-head research of one drug therapy over another—a completely valid outcome if that were the only condition of success. However, if the patient never engages in the compliance—never takes the drug—then the head-to-head superiority of the drug is a moot point. While we have written extensively on the engagement challenges for health improvement, the purchasing decisions for drugs have been based most often on formulary-based contracting.

Yet rebate-based contracting ignores comparative effectiveness of the drug and is built on unit-cost pricing, the very essence of commoditization.

Plan sponsors are emerging who will readily engage in an outcomes-based contract that promotes the improved health of the population. If the drugs are essentially equivalent for adherence and price, then the unit pricing may be the best contracting for the patient, for the plan sponsor, and for the pharmaceutical company. But if there is truly a difference in outcome—and we all know that not every patient is compliant, not every clinician knows who is most likely to be compliant—then assistance that could speed adoption of the appropriate intervention for the appropriate population group would be welcomed as assistance to the plan sponsor who must determine co-pays and adherence programs for any population.

It is fundamentally true that the health status of the population cannot be measured nor modified without the consideration of the economic impact of the condition to the total health of population. By targeting our resources more effectively to those most at risk for failure to manage their health, our families and our businesses can get economic relief. This, in turn, would promote healthier communities and reset our country on the track for total health and productivity. Achieving early wins of health and economic improvement can be attained by using more of the information that we already have, and rewarding those who share that information by contracting based upon those outcomes. For an example, consider the impact of adherence to the medication on the reduction of unnecessary rescue services—this often happens when diabetic patients become compliant with their hypertension medications, as seen in the reduction of renal stress/emergency room visits. Therefore, a contract could be constructed that joins the improvement in the adherence rate of hypertension management, rewarding the patients with lower out-of-pocket costs for the adherence, while also rewarding the physicians for higher adherence rates and lower emergency service use.

When the alignment of rewards across the health value chain is achieved, America will reap the rewards of improved financial and health stability. This alignment of rewards for improved health status (hypertension is controlled), improved care management (clinicians are managing their under-managed patients better), health plans and plan sponsors are deriving lower medical costs and better productivity, and manufacturers can share in the cost savings through gain-share) is the promise of linking CER with VBD, and not a moment should be wasted.

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PROFILE OF DR. ANNE CASTOT

Dr. Anne Castot serves as Head of Department, Risk Management and Information on Medicinal Products, for the French Health Products Safety Agency (Afssaps).

Q&A Would you please overview your career and the path it has taken?

I am a physician and a pharmacologist, specialized in public health. I started my activities in the area of medicinal products in the hospital more than 35 years ago. I was involved at the beginning of the organization of pharmacovigilance in France because I was already working in one of the first pharmacovigilance regional centers, created in 1974-75. I've been involved in the area of pharmaceuticals since then.

I worked first as a hospital practitioner until 1993, when the French agency was created. I was then asked by Pr. Jean Michel Alexandre to join the agency and organize its pharmacovigilance activities.

I had already had some exchanges with industry, especially when I was rapporteur for the pharmacovigilance dossier. It is part of the duties of the rapporteur to have some contact with companies so as to understand the safety data available and to develop the pharmacovigilance activities.

Since 1993-94 I've been head of the pharmacovigilance unit, then head of all the vigilance under Afssaps responsibility. Now, as head of the risk management sector, I have a lot of contact with industry, not only for discussing the dossier but also for regulatory organizational matters and so on.

I was the first French pharmacovigilance representative and have helped develop the pharmacovigilance working party at the European Medicines Agency since 1995. Then I became acting chairperson of the pharmacovigilance working party between 2001 and 2005, and I'm still a member specialized in risk management in the pharmacovigilance working party of the CHMP of the European Medicines Agency.

Q&A Where did you take your undergraduate and graduate training?

I started as a physician. I have been a doctor since 1975 and went directly to a university hospital as a resident, an assistant at the hospital, and then I took on some studies in public health, toxicology, and pharmacology, in Paris.

I started with clinics and will end as a regulator. I left the hospital definitively in 1993–94, although I tried to keep one half-day of consultation at the hospital. Besides all the studies and activities I had, I also studied and earned a certificate in epidemiology and studied statistics, but it was not sufficient. Knowledge and practice of epidemiology, as well as other new sciences, is needed to really handle properly all pharmacovigilance issues, such as statistics, and the mathematics that show what is needed for automated signal detection.

This is the message that I would like to give to my team: When all my pharmacists and doctors are working with me, I try to convince them to take some training in epidemiology and biostatistics, because it is essential.

Q&A What is the most important change that you've seen in your work environment?

The most important point to me is that industry and regulators together are making efforts to improve public health, not only by putting products on the market but also by monitoring the benefit/risk of the product. Traditionally, the company's responsibility was to develop drug products and put new medicinal products into the marketplace, and the regulatory authority or medicines agency was in charge of protecting the public health. However, it is good that the duty of both parties rises above that. Clearly, the feeling now is that we are in it together, and that the most important objective for us is to develop new strategies for new products to improve public health.

Recently, I met with a company about an orphan drug, to ensure that the product will be safe and that it really has a benefit for this population. I feel that if I went back 20 or 30 years, my most important concern would have been to monitor the product and identify its safety profile as soon as possible, but not really to check how we can minimize the risk, evaluate the impact of minimization measures, and whether patients and health professionals were satisfied with all the actions we took. Today, it's a more global approach, not only how to make the benefit/risk discoverable and able to be monitored; it's actually a wider, more strategic approach for treating and protecting patients.

Q&A How much satisfaction have you found in your career so far?

There are three parts to my career. The first part was at the hospital, and the second part was the development of pharmacovigilance at the agency level. The third step that I'm taking now is different: It's my responsibility to develop the risk management strategies at the agency level for medicinal products, including cross-relationships with many institutions and agencies in charge of patient safety. All three periods were different, but equivalent in terms of my satisfaction. I think I had a chance to have a very balanced career between the hospital, as the first scientific expert when I came to the agency to organize pharmacovigilance and really evolve the technical scientific issues in the dossier, and now more or less as a regulator and a manager. I think that since the beginning of my career, I have been part of some new areas, and that is very satisfying for me.

Q&A Why and how have you found time to serve as a DIA volunteer?

At the very beginning, when I first arrived at the agency as a regulator, it was very beneficial to have some contact with industry. One way to do that is to participate in this type of volunteer activity and to exchange with other stakeholders, not only regulators but also through meetings at the agency, with companies concerned about a specific issue. I was first involved in the ICH E2C as a rapporteur for Europe, and it seemed normal that I could contribute my elaboration of the EU Guidance and share my views with companies or other stakeholders. It's clear that you have to share your time between many things: Management, which comes first for me because it's very important; my responsibility as a specialized expert at the EU level; then to keep some time free to meet with these stakeholders, sponsor companies, patient representatives, or health association representatives. One way to meet with them is to go to different meetings or congresses, such as those offered by DIA. I certainly recognize that there is so much work that I cannot participate in DIA meetings in Europe as often as I would like.

Q&A How do you manage to balance the time you need for your professional life with the time you need for your personal life?

I am a very bad example, very bad. It was probably easier when I arrived at the agency because we did not have the workload that we have now. But I confess that I take only two or three weeks a year for holiday. But when executives accept our level of responsibility, we should do what we can do – you cannot say "no." The H1N1 pandemic is probably one reason for the workload and agenda because we have a lot of meetings, a lot of requests for exchanges with the Ministry of Health. It is totally full and crazy; it's probably the same for executives in other agencies. I confess that I have from five to eight meetings per day, and I have to prepare for these meetings. So, as you can imagine, I have to wake up very early in the morning so that when I arrive at the agency I can work alone. I need to work in the quiet, without the phone and mobiles and email, just to prepare my dossier, my interventions, my lectures, and so on. I should find some time to prepare for the future because I will probably retire in five or six years.

Q&A How does the work that you do impact the lives of patients in Europe?

My job is to manage the safety of medicinal products after they've been approved for marketing. The main objective of this is to protect public health, it seems to me. This means that each time we identify a safety signal, we take minimization actions. We take these actions not to save the product but to protect patients and consumers. It's a reality. I think that the main objective of our work, whether we do scientific evaluations, collect and evaluate data, put epidemiological studies in place, or conduct signal detection, at the end is to optimize the benefit/risk profile of the product and to protect the public and patient health. ■

Dr. Jeff Goldsmith to Chair CER Multitrack Plenary

As the cost of medicines and health care technologies continues to challenge personal, national, and global economies, creating a worldwide, patient-centered and consumer-driven health care marketplace also becomes more important. Comparative effectiveness research (CER) and related health technology assessments (HTAs) have become essential tools in quantifying these costs, and the relative value of the benefit that they return to the patients and societies who pay for them. CER and HTAs are also important aspects of the current health care reform debate in the US.

This year's Annual Meeting will explore global experiences with CER and HTA through a special **Multitrack Plenary Session: Implications of Comparative Effectiveness Research for Health Care Innovation**, presented at 8:00 AM on Tuesday June 15. The impact of CER and HTA on health care policy, pharmaceutical and device innovation, and ultimately better and more efficient patient care (in terms of both time and money) will be discussed by an executive panel of international leaders on health outcomes and reform. This panel will be chaired by Dr. Jeff Goldsmith, Associate Professor of Public Health Sciences at the University of Virginia; and President, Health Futures, Inc.

Dr. Goldsmith has lectured on health services management and policy at the Graduate School of Business of the University of Chicago (where he earned his doctorate in sociology), the Harvard Business School, the Wharton School of Finance, Johns Hopkins, Washington University, and the University of California at Berkeley. In 1990, Dr. Goldsmith received the Corning Award for excellence in health planning from the American Hospital Association's Society for Healthcare Planning. He is also a three-time recipient of the Dean Conley Award for best health care article from the American College of Healthcare Executives, and currently serves on the editorial board of *Health Affairs*.

After delivering his Keynote Address, Dr. Goldsmith will introduce and serve as session chair for the group discussion of CER and its implications by the featured expert panelists *(see accompanying box)*. He also shared his thoughts on the current and future states of CER and their potential impact on the health of the world's patients, societies, and economies, in the following Q&A with the *Global Forum*.

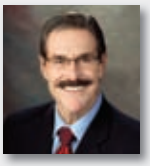
Q&A

***Wikipedia* defines Comparative Effectiveness Research as "The direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms. The core question of comparative effectiveness research is which treatment works best, for whom, and under what circumstances." How do you define it?**

Featured CER Multitrack Panelists:

In addition to Dr. Goldsmith, this discussion panel will feature:

Richard Gliklich, MD President & CEO, Outcomes Sciences, Inc., US



Jack Lewin, MD Chief Executive Officer, American College of Cardiology, US

Mark B. McClellan, MD, PhD Director, Engelberg Center for Health Care Reform, Brookings Institute, US

Michael D. Rawlins Chairman, National Institute for Health & Clinical Excellence (NICE); University of Newcastle; UK

David B. Snow, Jr. Chairman of the Board & Chief Executive Officer, Medco Health Solutions, Inc., US

Myrl Weinberg President, National Health Council, US

My principal focus is understanding how technologies are assimilated into and used in the health care system. CER means trying to understand the incremental contribution of a new technology to improving the health of a population of people, and what is the return to society of bringing that technology into being, based on those improvements. It is rare that we get a new drug or a new diagnostic technology that is completely novel in its effect on clinical decision making or clinical outcomes. CER attempts to create a data-based way of evaluating whether it makes sense for society to pay for it or not, and how much to pay for it, and, most importantly, whether clinicians should use these tools in their practices.

Q&A What educational background or professional experiences led you to this career path?

I have an academic doctorate in sociology. I studied sociology of professions and of complex organizations in my work at the University of Chicago, but my first job out of graduate school was as a policy analyst and researcher for the governor of Illinois. So I entered the policy world directly from school, and I entered health care, really, as a lobbyist for the University of Chicago Medical Center, a large academic health center. We had a clinical faculty at that time of over 600 people and a huge biomedical research operation.

My first exposure to all of this was trying to be an advocate for those scientists and clinicians to make sure that state and federal governments didn't just gut our funding base. To understand what an academic health center did, I had to go into operating rooms and laboratories and ask a whole bunch of stupid questions like, "What do you do?" That was my first exposure to medical technology and clinical practice, and it was absolutely fascinating. A lot of mentors and teachers in our clinical faculty were really interested in these issues and wanted to make sure, as we made our case in Springfield and Washington, that we could explain what government was getting out of investing in us. That's where my interest in biomedical research and evaluation came from, more than 30 years ago.

Q&A Haven't private insurance companies been doing something very similar to CER for years – what's new?

Different audience with a different objective. The ultimate goal of CER is to give clinicians the knowledge to make better decisions about which technology to use when. The proximate goal is to provide an evidentiary basis for coverage and payment policy. The goal of health insurance based CER is to decide whether a specific health plan should cover a technology and what to pay for it. In a sense, you're sort of getting at the same issue: "Does this technology really make a difference?" But in the health plan instance, you really are focused on policy making for a specific organization and its population of subscribers. CER focuses on society as a whole, and is ultimately about reshaping clinical practice.

Q&A The National Institute for Health & Clinical Excellence (NICE) agency has been involved in similar efforts in the UK: Do the different legislative or regulatory environments between the US and the UK impact these activities?

Ultimately, this process is intensely political because it affects both the incomes of the practitioners who conceivably may use the technology, as well as the revenue streams of the companies that invented them. The process in Britain is not apolitical, but at least there is sufficient consensus that you need a scientific basis for making payment decisions, which led to the creation of NICE. Sir Michael Rawlins of NICE will participate in our panel at this upcoming Annual Meeting.

Whatever government or society you're dealing with, CER still raises complex political and economic issues with major consequences for both practitioners and companies. There is intense and focused patient and family advocacy for many of these technologies, and an increasing suspicion of governments controlling access to those technologies. There's an expression that Social Security is the "third rail" of American politics – touch it and you die. Increasingly, access to technology is a "third rail" in our political system because people are so intensely suspicious that government's real motivation is to save money at the expense of patient access, not to assure better and more evidence based clinical decision making.

If the environment is so politicized that scientific facts don't matter in how we make policy, we really are in deep trouble. The fact that people do not trust not merely the government but the scientific community to make objective and thoughtful decisions about what is and isn't helping us really puts us in a very difficult position. To me, at its root, decisions about a $2.5 trillion health system have to be based on facts.

Q&A Looking forward, two or three years from now, what will some of the CER "hot topics" be?

I know from my book research on imaging that we're going to get new

tools in molecular diagnosis that will give us the ability to define biological processes from the imaging suite that we used to rely on the clinical lab to understand. We're going to be given a whole new and very expensive toolset of molecular tags and therapeutic tools. I think that this array of new tools is going to be very controversial because they are going to be expensive. Certainly, in the scientific arena, I see molecular imaging as one of the "hot spots" that we're going to need help from CER to evaluate.

But the biggest issue is going to remain the political issue. Health reform is dangling by a thread as we conduct this interview. One of the White House's biggest priorities in this process has been to make sure that we have a robust comparative effectiveness process that we can rely on in the next decade to help make better and more thoughtful coverage and payment decisions for Medicare. If we don't get that, I think we really are going to be wielding pickaxes rather than scalpels in deciding how to pare back the rate of growth in health spending.

In the next two to three years, we are going to be in serious deficit reduction mode: Are we going to make deficit reduction decisions that affect how we spend our Medicare and Medicaid dollars based on facts, or is it simply going to be some rugby scrum where the people who push the hardest get what they want, at the expense of others who are not as well organized? Do we have scientific based health policy, or do we have brute force based health policy? To me, that's the biggest single issue, and I think we're going to be right in the middle of it in the two- to three-year horizon that you ask about.

Q&A What did we NOT ask you that you wish to share with DIA?

What I'm hoping comes out of this controversy about our health system is the realization that we're only a part of the way to the science and knowledge base that we need to truly affect the major health risks of our population. We really need to invest not only in basic research but in the type of applied research that includes comparative effectiveness to really get to a health system that we can afford and be proud of. ■

Q&A with Annual Meeting Program Chairperson

Gaby Danan

Part 2

The volunteer program committee, session chairs, and speakers continue to prepare for our upcoming 46th Annual Meeting – June 13–17 in Washington, DC – under the leadership of Annual Meeting Program Chair Gaby Danan, MD, PhD (sanofi-aventis, France). "I think it's a great experience," Gaby said. "This is an open forum for everybody in any biopharmaceutical industry interest area, or regulators of that industry, to make progress in developing their own career. There are other not-for-profit associations, especially in the area of regulatory affairs, but they only focus on one part – an important part, certainly – of this industry sector. But the wide range of our industry's activities is really represented only at the DIA Annual Meeting." Gaby shares additional thoughts about our industry's most comprehensive and respected annual event below.

Q&A What does the selection of someone from outside North America to serve as program chairperson for DIA's flagship meeting in North America say about DIA's global reach?

It is a big honor for me to chair the program. This is evidence that DIA is a truly global organization. I am not the first European to chair the Annual Meeting – I think I am the third, but this means that DIA considers issues regarding the biopharmaceutical industry as global and not only regional. This is also a good foundation for people from other regions of the world to also serve as chair of the DIA Annual Meeting – why not somebody from China or India in the near future?

Q&A What highlights have the Program Committee planned for this year's Annual Meeting?

The new FDA Commissioner, Dr. Margaret Hamburg, will be attending to deliver the Keynote Address on topics closely related to our Annual Meeting theme; locating our meeting in Washington DC puts us close to the FDA and research centers such as the NIH (National Institutes of Health). I would also like to emphasize that we have created what we call "Mini Multitracks" where one topic can be cooperatively addressed across several tracks in order to put several aspects of that same topic in perspective. Other highlights include the participation of patient associations, who have been invited into several sessions, which is rather new for DIA, as well as our annual opportunity for professionals and in for students, to have an adjudicated poster session and be rewarded for their efforts.

It is also extremely important to visit the exhibit hall. We will offer this year, as last, an extended period of time to go to these exhibit booths. For those of us who work in industry, it is important to meet the companies staffing these booths to discuss the new devices, new technologies, new approaches, and new services they can offer. In our daily work, it is essential to have this kind of information directly from these professionals; this offers a unique opportunity to speak with many of them in the same place at the same time.

Q&A As an industry professional, what does the opportunity to participate in a neutral, open forum mean to you?

The main purpose of DIA is to provide this neutral forum. It is critical to give regulators the opportunity to attend this kind of meeting, and to give other attendees who come from industry or other organizations the opportunity to meet regulators. This is also an opportunity for regulators to exchange their experiences, not only among themselves but also with other participants. The main objective of DIA is to provide this forum for all the stakeholders in the biopharmaceutical industry. This is critical for our attendees' professional future.

How long have you been attending the Annual Meeting, and how has it benefitted you and your colleagues?

I have been attending the DIA Annual Meeting for more than 15 years, maybe half of them as a member of the Board of Directors and the other half as a DIA member. I really enjoy attending this meeting, not only for the networking opportunities but because we can share our best practices, our knowledge, and our experience, with other colleagues. It is always reassuring to have this kind of opportunity to exchange this kind of information with colleagues, because at the end of the day we are facing the same issues and we need to know how our colleagues have discovered their solutions to these issues. Having this network is really great for our day-to-day work.

I would add that this meeting presents an opportunity for attendees to become DIA members and join one of our Special Interest Area Communities (SIACs), which is a great way for them to exchange information with colleagues in their specific professional discipline, and to propose themes for new DIA programs, training courses, or webinars. Through this involvement, step by step, they can become experts in their particular area and facilitate their communication with other colleagues.

The DIA Annual Meeting attracts representatives from regulatory agencies literally all around the world. What makes this event unlike any other industry event, and so attractive to all sectors of the biopharmaceutical industry?

The biopharmaceutical industry is highly regulated. It is important, then, to exchange information and to maintain dialogue with these regulators. To maintain this dialogue, we need a forum. This forum is provided by DIA. This is a neutral forum, provided by a not-for-profit organization, which is absolutely essential, because regulators see that their presence cannot be interpreted as part of a promotional presentation but as an open dialogue with everybody. This makes us unique – the fact that regulators from all over the world come to DIA to speak with their colleagues from, and share knowledge with, other agencies, and also to share knowledge with the biopharmaceutical industry about the issues that they regulate. Because DIA provides a neutral forum, these conversations are not for or about a specific product or an issue specific to one company, but more general issues that involve the industry as a whole. We can ask regulators questions about the rationale behind their decisions, which is sometimes not quite understood, and also about future regulatory trends. Forthcoming regulatory changes can be critical for companies, because some of these changes can require additional investments or organizational changes.

Why is DIA's relationship with the European Medicines Agency (EMA) so strong, and why is it important to continue to cultivate this relationship?

In Europe, probably more than in any other region, we need harmonization between the countries. The European Medicines Agency has a role in coordinating more than 27 regulatory agencies in Europe. DIA provides the forum for this one main regulator – the European Medicines Agency – to discuss issues with all stakeholders. DIA not only provides this kind of forum, we provide several DIA/European Medicines Agency collaborative training courses, especially in my area of interest, which is pharmacovigilance.

Why is DIA so valuable to professionals who live or work in Europe?

In Europe, DIA has a big role in organizing meetings between regulators and industry. We need a lot of harmonization between the agencies in Europe, and the European Medicines Agency expends a lot of effort to achieve this harmonization. We who work in companies in Europe face different issues in different countries. So to create some harmonization, and make communication between these countries easier, it is important to invite them to come together to make sure that there is smooth dialogue not only between them, but also with industry.

What do you enjoy the most about DIA's annual flagship event in Europe, our EuroMeeting?

We very much look forward to every EuroMeeting, because this is the only time for most of the people who work in the biopharmaceutical industry, and regulators, to exchange knowledge about current regulations, best practices, and future regulations, at the highest level in Europe. It is important for people working in industry to receive this kind of information directly from regulators, to understand future trends and the rationale behind current regulatory changes.

What advice would you offer to someone to help

them navigate through their first Annual Meeting?

A: Probably the most important advice is to look through the final program before coming to the meeting; you have the opportunity to consult this program on the DIA website, where it is updated regularly. Go through the first pages of this program to read all the session titles, which are also annotated by professional interest area. Then you can make your choice about what sessions to attend, and plan your navigation around that. One of the more novel aspects of this year's meeting is the creation of our "Mini Multitracks" where the main topic will be developed at the highest level and be discussed in more detail in subsequent sessions. This kind of navigation between the sessions is also explained in the program, so that every individual can make his or her own way around their areas of interest. ■

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UPCOMING EVENTS

In the Americas

Conferences

APRIL 18-21, 2010
4th Annual FDA/DIA
Statistics Forum
Bethesda, MD

JUNE 13-17, 2010
46th DIA Annual Meeting
Washington, DC

SEPTEMBER 30 – OCTOBER 1, 2010
2nd DIA Conference for
Harmonization of Risk
Management Plans
Washington, DC

Training Courses

MAY 3-5, 2010
Drug Safety Surveillance
and Epidemiology
Horsham, PA

MAY 5, 2010
Introduction to Signal Detection
and Data Mining
Horsham, PA

MAY 6-7, 2010
Using Risk Management
Programs to Enhance the
Safety of Medicines
Horsham, PA

MAY 6, 2010
How to Prepare for a Safety
Inspection
Horsham, PA

AUGUST 9-12, 2010
Leadership Experience
Boston, MA

AUGUST 9-13, 2010
Regulatory Affairs Part I: The IND
Phase and Part II: The NDA Phase
Boston, MA

AUGUST 9-10, 2010
European Regulatory Affairs
Horsham, PA

SEPTEMBER 13-15, 2010
Regulatory Affairs Part I:
The IND Phase
Horsham, PA

SEPTEMBER 20-22, 2010
Drug Safety Surveillance and
Epidemiology
Horsham, PA

Europe

Conferences

MAY 28, 2010
Polish and European Regulation:
Free Hot Topic Workshop
Organised by the DIA Advisory
Council of Europe
Warsaw, POLAND

JUNE 1-2, 2010
European Regulatory Affairs
Forum 2010
London, UK

SEPTEMBER 27-29, 2010
Workshop on Statistical
Methodology in Clinical R&D
Vienna, AUSTRIA

Training Courses

MAY 5-7, 2010
Essentials of Clinical Study
Management
Vienna, AUSTRIA

JUNE 2-4, 2010
Practical Guide for
Pharmacovigilance: Clinical Trials
and Post Marketing
Prague, CZECH REPUBLIC

JUNE 3-4, 2010
European Regulatory Affairs
Prague, CZECH REPUBLIC

JUNE 3-4, 2010
Crisis Management
Basel, SWITZERLAND

JUNE 4, 2010
Advanced GCP Study Monitoring
Prague, CZECH REPUBLIC

JUNE 25, 2010
European Medicines Agency
Information Day: The New
Individual Case Safety
Report (ICSR) International
Standard and ICH E2B/M2
London, UK

SEPTEMBER 13-14, 2010
Medical Approach in Diagnosis
and Management of ADRs
Paris, FRANCE

SEPTEMBER 13-14, 2010
Clinical Statistics for Nonstatisticians
Paris, FRANCE

Japan

Conferences

MAY 25-26, 2010
1ST Cardiac Safety Workshop
Tokyo, JAPAN

OCTOBER 28-29, 2010
7th DIA Japan Annual Meeting
Tokyo, JAPAN

Training Courses

JUNE 2010
3rd DIA Regulatory Affairs
Training Course in Japan
Tokyo, JAPAN

46th DIA Annual Meeting

Facilitating Innovation for Better Health Outcomes

June 13-17, 2010
Washington, DC

Walter E. Washington Convention Center

Your Guide to the Annual Meeting

DIA®
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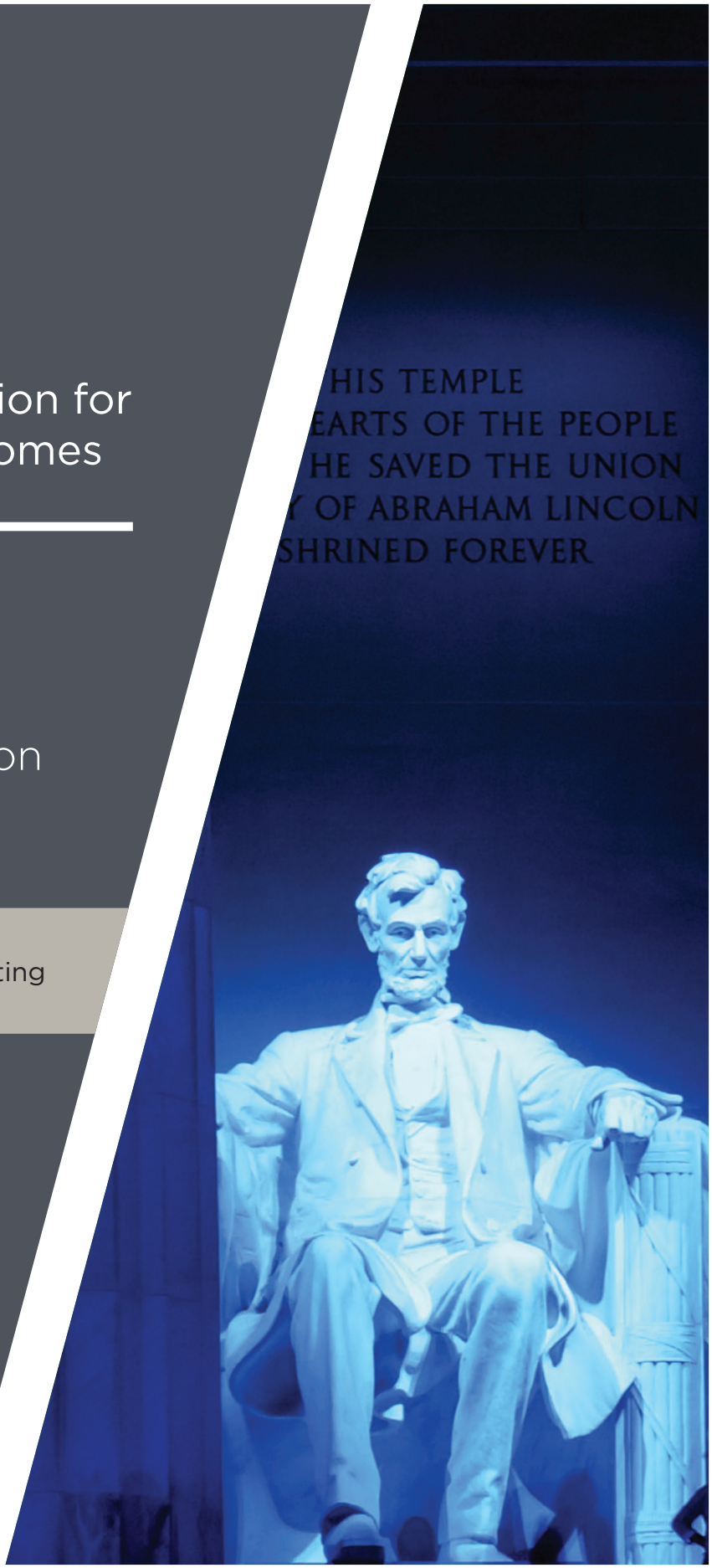


GLOBAL SCOPE
KNOWLEDGE
INNOVATION

The DIA Annual Meeting is the premier event for professionals involved in the discovery, development, and lifecycle management of pharmaceuticals, medical devices, and related products. There is no other industry meeting of its kind that can rival the breadth and depth of experience that this meeting delivers. With 25 content-area tracks, 350 sessions and 20 tutorials, presentations are geared to attendees at all disciplines, works settings, and experience levels. The DIA Annual Meeting, above all others, offers valuable professional cross-functional learning and networking experiences.

HIGHLIGHTS

- 8,000+ professionals from 80 countries
- 20+ global regulatory agencies
- 350+ sessions in 25 content-area tracks
- 20 pre-conference tutorials *(see back panel for more information)*
- 550+ exhibiting companies
- Student and Professional Poster Sessions
- Networking Reception: Sunday, June 13, 7:00 - 9:00 PM at the Newseum

"The DIA Annual Meeting is like having the world of what we do in one venue."

MUST-ATTEND SESSIONS

Keynote:
Margaret A. Hamburg, MD, Commissioner, US Food and Drug Administration

Keynote:
Jeff Goldsmith, PhD, University of Virginia; President, Health Futures, Inc.

Monday, June 14

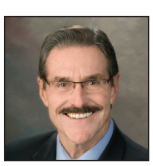
8:30 - 10:00 AM — **Opening Plenary Session Featuring Keynote Address by Dr. Margaret A. Hamburg**

Tuesday, June 15

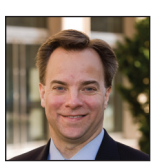
8:00 - 9:30 AM — **Multitrack Plenary Session: Implications of Comparative Effectiveness Research for Health Care Innovation**

A high-level panel will present perspectives on what is required to develop and maintain a comparative effectiveness research and health technology assessment program with the end result of better and expedited care for the patient. This session will explore the global experience with comparative effectiveness research and health technology assessment by examining the issues that the global medical community should consider as it strives for a patient-centered and consumer-driven health care marketplace.

Richard Gliklich, MD, Outcome Sciences Inc.



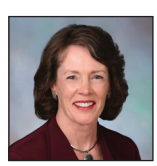
Jack Lewin, MD, American College of Cardiology



Mark B. McClellan, MD, PhD, Engelberg Center for Health Care Reform, Brookings Institute

Michael D. Rawlins, NICE; University of Newcastle, UK

David B. Snow, Medco Health Solutions, Inc.



Myrl Weinberg, National Health Council

Earn Continuing Education Credits for tutorials and sessions. Visit www.diahome.org/annualmeeting for details.

AD – Advertising

MONDAY | 10:30 AM
Is Industry-supported Education the Next Taboo?

MONDAY | 1:30 PM
Pharmaceutical Marketing Primer

TUESDAY | 8:00 AM
FDA Enforcement Update: Regarding Advertising and Promotion

TUESDAY | 10:00 AM
Update on Direct-to-consumer Advertising (DTC)

WEDNESDAY | 8:30 AM
Social Media and the FDA Guidance Document

AHC/IS – Academic Health Centers/Investigator Sites

MONDAY | 10:30 AM
Multiregional Clinical Trials: It Takes a Global Village of Expertise

MONDAY | 1:30 PM
How Investigator Budgets Impact Patient Enrollment and Retention

MONDAY | 3:30 PM
IRB Qualifications

TUESDAY | 10:00 AM
Use of Patient-targeted Informatics for Minority Recruitment Into Clinical Trials

TUESDAY | 2:00 PM
Collaborative Approaches to Product Discovery, Development, and Evaluation

TUESDAY | 4:00 PM
Operationalizing ACPU Standards in an Evolving Early-phase Environment

CRO and Sponsor Perspectives on the Challenges of Site Selection

WEDNESDAY | 8:30 AM
Investigators Needed! Why Clinical Research Should Be Part of Your Practice

WEDNESDAY | 10:30 AM
About SChMiDTS: Sponsor Investigator and Clinical Investigator Requirements for Medical Device Trial Submissions

WEDNESDAY | 1:30 PM
Responding to FDA/OHRP Training Requirements for Investigators and Institutions

WEDNESDAY | 3:30 PM
Quality and Performance in Clinical Research: Establishing a Quality Management System for Success

THURSDAY | 8:30 AM
Investigative Sites and CROs: Working Together Toward One Common Goal

THURSDAY | 10:30 AM
Capacity Building Initiatives in Emerging Markets: Is Principal Investigator Training the Answer?

BT – Biotechnology

MONDAY | 10:30 AM
Hot Topics in Biotechnology

MONDAY | 1:30 PM
Gaining Critical Efficiencies in Biotechnology Drug Development Through Global Regulatory Strategies

MONDAY | 3:30 PM
Global Lessons Learned from Development of the Pandemic (H1N1) 2009 Vaccine

TUESDAY | 8:00 AM
International Nonproprietary Names (INNs) for Biological Substances

TUESDAY | 10:00 AM
Challenges in Bringing Novel Cell-based Therapies

TUESDAY | 2:00 PM
Gene Therapies: Technology

TUESDAY | 4:00 PM
Gene Therapy: Regulatory Pathway for Clinical Development

WEDNESDAY | 8:30 AM
Comparability of Biological Medicines Following Process Change

WEDNESDAY | 10:30 AM
Progress Towards a US Regulatory Pathway for Follow-on Biologics

WEDNESDAY | 1:30 PM
Recent Advancement of Follow-on Biologics in Asian Pacific Region

WEDNESDAY | 3:30 PM
Immunogenicity Assessment for Therapeutic Proteins

THURSDAY | 8:30 AM
Next Generation Biologics: Deimmunization and Tolerance Induction

THURSDAY | 10:30 AM
Can We Build Better Vaccines Using Adjuvants?

CDM – Clinical Data Management

MONDAY | 10:30 AM
Experiences with the Use of CDISC-controlled Terminology in Pharmaceutical and Clinical Research

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research or Transform It?

MONDAY | 3:30 PM
Misusing EDC: Bad Examples and How to Fix Them

TUESDAY | 8:00 AM
Partnering in Outsourced Data Management: Measures to Better Align Performance Expectations

TUESDAY | 10:00 AM
Electronic Health Records (EHR) and Data Management

TUESDAY | 2:00 PM
The Future of Data Management

TUESDAY | 4:00 PM
EDC Hot Topics: A Panel Discussion

WEDNESDAY | 8:30 AM
Electronic Data Capture in Phase 1: Do the Pros Outweigh the Cons?

WEDNESDAY | 10:30 AM
What Deliverable? Importance of Close Collaboration Between Data Management and Other Functions

WEDNESDAY | 1:30 PM
How Do We Prepare for Database Lock? Readiness of Sites, CROs, and Sponsors

WEDNESDAY | 3:30 PM
CDASH Standard CRFs: Everyone's a Winner

THURSDAY | 8:30 AM
Clinical Database Audits: Past, Present, and Future

THURSDAY | 10:30 AM
Hot Topics in ICH: MedDRA®, Revision of Individual Safety Reports (E2B-ICSR), and Identification of Medicinal Products (M5-IDMP)

CMC/GMP – Chemistry, Manufacturing, and Controls/ Good Manufacturing Practices

TUESDAY | 8:00 AM
Preapproval Inspection Requirements

TUESDAY | 10:00 AM
Quality-by-design for Biotechnology

TUESDAY | 2:00 PM
Updates on ICH Quality Topics

TUESDAY | 4:00 PM
Global Perspectives on API (Active Pharmaceutical Ingredients) Quality – Collaboration on Inspections

WEDNESDAY | 8:30 AM
Challenges in the Implementation of Quality-by-design Across the Pharmaceutical Industry

WEDNESDAY | 10:30 AM
Quality-by-design: Linking Quality to Safety and Efficacy – Part 1 of 2

WEDNESDAY | 1:30 PM
Quality-by-design: Linking Quality to Safety and Efficacy – Part 2 of 2

WEDNESDAY | 3:30 PM
Combination Products: Regulatory and Quality Aspects

THURSDAY | 8:30 AM
Supply Chain Security

THURSDAY | 10:30 AM
Drug Master Files: Regulatory Aspects

CR/CS – Clinical Research and Development/Clinical Supplies

MONDAY | 10:30 AM
Multiregional Clinical Trials: It Takes a Global Village of Expertise

Visit www.diahome.org/annualmeetingsessions for up-to-date information.

CR/CS – Clinical Research and Development/ Clinical Supplies continued

MONDAY | 1:30 PM
Who Is Accountable for Site Selection and Patient Recruitment?

Cracking the Globalization Code

The Future of Oncology Clinical Development: Key Findings

Understanding the Benefits and Limitations of Drug Pooling

Fiscally Responsible Protocol Development

MONDAY | 3:30 PM
Is this Trial Enrollable? Defining Recruitment Feasibility

Clinical Research in Asia: Beyond Confirmatory Trials

Centralized Monitoring: When Does It Make Sense?

Perspectives of the IRB Process in Phase 1 Studies Conducted in an Academic Setting

Clinical Trials: The Race to Study Launch and Speed to Finish

TUESDAY | 10:00 PM
Creating an Interactive Connection Between Clinical Strategy and Clinical Operations

Fostering Global Collaboration Through Adoption of a New Enrollment Planning Culture

Incorporating Risk Management Strategies Into Premarketing Clinical Trials

Phase 1 Clinical Safety: Subjects and Signals

TUESDAY | 2:00 PM
Recognizing the Potential of the Site

The Ripple Effect in Clinical Trials

Clinical Projects: Faster and Smarter? It's All in the Planning!

TUESDAY | 4:00 PM
When Senior Management Says "Prove It!": Can You Articulate Patient Recruitment ROI?

Global Trials on a Budget: How Small to Mid-size Companies Can Get Quality Data

Adaptive Trials: Too Complicated for Little Return?

WEDNESDAY | 8:30 AM
Rethinking the Study Feasibility Assessment Process to Ensure Successful Implementation

Clinical Trials in the Age of Personalized Cancer Medicine

Solving the Clinical Supplies Challenges for Adaptive Trials

How Many Clinical Trial Managers Does It Take to Manage a Trial?

WEDNESDAY | 10:30 AM
New and Evolving Patient Recruitment and Retention Practices

The Added Value of Including Emerging Markets in Global Clinical Trials

Pediatric Medicines: Communication to Bridge the Gap Between Regulations and Feasible Trials

Investigator Initiated Trials (IIT)

WEDNESDAY | 1:30 PM

Site Relationship Management (SRM) Initiatives for Improving Site Performance

Stretching the Clinical Dollar in Challenging Financial Times

Living in a Virtual World: Virtual Solutions to Real Study Problems

Using eClinical Metrics of Protocol Compliance for Planning and Managing Trials

WEDNESDAY | 3:30 PM
Patient Recruitment in a Technological Era

Assessing and Measuring Performance in Clinical Research

Increasing Importance of Independent Data and Safety Monitoring in Clinical Research

THURSDAY | 8:30 AM
The Mechanics of Virtual, Global Communication: Executive Perspectives

THURSDAY | 10:30 AM
Impact of Productivity Transformation Initiatives on Clinical Site Monitoring Processes

CSP – Clinical Safety and Pharmacovigilance

MONDAY | 10:30 AM
The FDA's Safe Use Initiative

MONDAY | 1:30 PM
FDA Sentinel Initiative: Year 2

Stretching Boundaries in the Use of Data Mining

MONDAY | 3:30 PM
New Business Models for Postmarketing Surveillance: Beyond ASTER

Balancing Computational Power and Clinical Prowess in Safety Signal Detection

TUESDAY | 10:00 AM
Risk Management Between the Regulatory Rock (FDA REMS, EU RMP) and the Litigation Hard Place

TUESDAY | 2:00 PM
Pharmacovigilance in Asia: The Japan, China, and India Perspective

TUESDAY | 4:00 PM
REMS Evaluations: What Have We Learned?

Modernization of FDA's Adverse Event Information Management Program

WEDNESDAY | 8:30 AM
Pharmaceutical Packages and New Safety Legislation in EU

Can a Risk Management Program Save a Product from Withdrawal?

WEDNESDAY | 10:30 AM
Clarifying Blinded and Unblinded Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting in US and Europe

WEDNESDAY | 1:30 PM
Evolving Paradigms in Pharmacoepidemiology

WEDNESDAY | 3:30 PM
Data Gathering and Communication Tools to Improve Safe and Effective Use of Drugs During Pregnancy and Lactation

Developmental Safety Update Report (ICH E2F)

THURSDAY | 8:30 AM
Designing a Global, Cross-functional Pharmacovigilance Solution that Focuses on Vigilance

THURSDAY | 10:30 AM
Due Diligence and In-licensing Opportunities with a Pharmacovigilance/ Safety Perspective

EBM – Evidence-based Medicine

TUESDAY | 8:00 AM
Implications of Comparative Effectiveness Research for Health Care Innovation

TUESDAY | 10:00 AM
PROs: Perspectives from an Oncologist, Regulator, and Patient

TUESDAY | 2:00 PM
Payer Perspectives of Evidence-based Medicine and Comparative Effectiveness

TUESDAY | 4:00 PM
Data Focused Collaborations: Challenges and Opportunities

EC – eClinical

MONDAY | 10:30 AM
Chaos and EDC: What to Avoid if You Possibly Can

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research or Transform It?

MONDAY | 3:30 PM
Standards-based Approach to Creating One Elegant Multisystem Solution

TUESDAY | 10:00 AM
Parallel Lines Eventually Intersect: Evolution of Technologies in Parallel Industries

TUESDAY | 2:00 PM
Monitoring the State of CDISC and HL7 Standards for Clinical Research and Regulatory Submissions

Earn Continuing Education Credits for tutorials and sessions. Visit www.diahome.org/annualmeeting for details.

TUESDAY | 4:00 PM
EHRs and Clinical Research: Update from the HL7 Working Team and the New ANSI Standard

WEDNESDAY | 8:30 AM
Electronic Source Documents: Removing the Paper Burden from Sites and Sponsors

WEDNESDAY | 10:30 AM
eInformed Consent: Putting the Pieces Together

WEDNESDAY | 1:30 PM
Quantifying Data Quality for eClinical Trials

WEDNESDAY | 3:30 PM
Innovations in Combining Patient-reported Outcomes with Physiologic Measurements to Leverage Real-time Access to Data

THURSDAY | 8:30 AM
Leveraging eClinical Technologies in the Conduct of Adaptive Clinical Trials

THURSDAY | 10:30 AM
CDISC Pilots

ERS/DM – Electronic Regulatory Submissions/Document Management

MONDAY | 10:30 AM
From EDMS to Collaboration: The Drive Toward Content

Multilingual Labeling in the Context of PIM

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research or Transform It?

MONDAY | 3:30 PM
Data and Document Due Diligence: What Is Being Done and NOT Done!

Electronic Laboratory Notebooks

TUESDAY | 10:00 AM
FDA Data Standards Initiatives

Life Cycle Management of European eCTDs

TUESDAY | 2:00 PM
CDER eSubmission Update: The Review Perspective

TUESDAY | 4:00 PM
CDER eSubmission Update: The Future State

WEDNESDAY | 8:30 AM
International eSubmission Standard

WEDNESDAY | 10:30 AM
Data Submissions to CDER: Getting It Right

WEDNESDAY | 1:30 PM
FDA's Electronic Registration and Listing System

Experiences with Outsource Partnering for eCTD Production

WEDNESDAY | 3:30 PM
Global Electronic Submissions

The EDM Reference Model: Current Use and Future Plans

THURSDAY | 8:30 AM
Pursuing Standards to Enhance eCTD Deliverables

THURSDAY | 10:30 AM
Global Submission Management: Improving Efficiencies in Working with Non-ICH Regions

EXEC – Executive Policy Forum

TUESDAY | 8:00 AM
Implications of Comparative Effectiveness Research for Health Care Innovation

TUESDAY | 10:00 AM & 2:00 PM
The New Landscape for Industry-profession Relations: From Policy to Practice – Part 1 and Part 2

GCP – Good Clinical Practice

MONDAY | 10:30 AM
Virtual Realities: Quality Considerations When Using Outsource Providers

Multiregional Clinical Trials: It Takes a Global Village of Expertise

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research or Transform It?

MONDAY | 3:30 PM
Computer Systems Compliance: Dealing with Computer Systems, Part 11, and EHR

TUESDAY | 10:00 AM
FDA and European Medicines Agency Update on GCP Inspections and the Conduct of Clinical Trials

TUESDAY | 2:00 PM
Defining Quality in Clinical Trials

TUESDAY | 4:00 PM
Conducting Clinical Trials in India and China: GCP Compliance and Maximizing Quality at Investigative Sites

WEDNESDAY | 8:30 AM
IRBs and Consent Form Readability

WEDNESDAY | 10:30 AM
Communication Dilemmas Among Clinical Sites, Sponsors, and Institutional Review Boards (IRBs)

WEDNESDAY | 1:30 PM
Recommendations for Industry-wide Adoption of Best Practices in Global Clinical Trials

WEDNESDAY | 3:30 PM
Quality Assurance Methods to Ensure Compliance in Global Biorepository Operation

THURSDAY | 8:30 AM
A High-quality Clinical Study: Whose Job Is It Anyway?

THURSDAY | 10:30 AM
FDA and Industry Perspectives for Effective Monitoring and Auditing of Clinical Trials

IT – Information Technology

MONDAY | 10:30 AM
Building a Next Generation Data Standards Metadata Repository

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research, or Transform It?

MONDAY | 3:30 PM
Channelling Metadata to Gain Control of the Clinical Trial Process

TUESDAY | 10:00 AM
Implementations of Data Element Dictionaries to Streamline Clinical Development

TUESDAY | 2:00 PM
Health Information Technology (HIT) and Personalized Medicine

TUESDAY | 4:00 PM
Integrating Process and Technology for an Efficient Document Processing Solution

WEDNESDAY | 8:30 AM
Life Sciences Cybercrime: A Law Enforcement Perspective

WEDNESDAY | 10:30 AM
Bringing Hosting, SaaS, and Cloud Computing to Clinical Research and Development

Biomedical Informatics in the New Global Pharmaceutical Model

WEDNESDAY | 1:30 PM
Using Data Governance to Cultivate Value

WEDNESDAY | 3:30 PM
Clinical Development Applications and Databases Integration Programs Update

Service-oriented and Event-driven Architectures

THURSDAY | 8:30 AM
Utilizing and Integrating Open Source Software in Clinical Research Environments

THURSDAY | 10:30 AM
Achieving Cost-effective Scalability in the Clinical Environment Through Cloud Computing

MA – Marketing

MONDAY | 10:30
Is Industry-supported Education the Next Taboo?

WEDNESDAY | 1:30 PM
Therapy Compliance: Good Practice in Any Practice

THURSDAY | 8:30 AM
Beyond Compliance: Self-regulation and Initiatives to Ensure Ethical Business Practices

MC – Medical Communications

MONDAY | 10:30 AM
Is Industry-supported Education the Next Taboo?

MONDAY | 1:30 PM
Pharmaceutical Marketing Primer

Visit www.diahome.org/annualmeetingsessions for up-to-date information.

MONDAY | 3:30 PM
Promotional Challenges Posed by Risk Evaluation and Mitigation Strategies (REMS)

TUESDAY | 2:00 PM
Medical Communications Roles at Scientific Medical Meetings

TUESDAY | 4:00 PM
Medical Communications Around the Globe

WEDNESDAY | 10:30 AM
Industry Support of Continuing Medical Education (CME)

WEDNESDAY | 3:30 PM
The Patient Perspective

THURSDAY | 10:30 AM
Online Health Information: The Rise of Health 2.0

MW – Medical Writing

MONDAY | 10:30 AM
Medical Writer Competency Model

MONDAY | 1:30 PM
Document Preparation When You're Short on Time

MONDAY | 3:30 PM
The Medical Writing Great Debate: Medical Writers SHOULD Be Scientists

TUESDAY | 10:00 AM
High-quality Regulatory Submission Documents

TUESDAY | 2:00 PM
Topic-based Content

TUESDAY | 4:00 PM
Clinical Study Report Appendices: For Better or Worse

WEDNESDAY | 8:30 AM
Reporting Safety Data in FDA Marketing Applications

WEDNESDAY | 10:30 AM
INDs with a Global Focus

WEDNESDAY | 1:30 PM
Authoring CTD/eCTD Submissions: Experience from FDA and Industry

WEDNESDAY | 3:30 PM
Global Strategies in Medical Writing: A Perspective from Asia

THURSDAY | 8:30 AM
Effective Publication Practices

NC – Nonclinical Laboratory Safety Assessment

TUESDAY | 4:00 PM
The Interplay Between Nonclinical Studies and Pharmacovigilance Activities

WEDNESDAY | 8:30 AM
Preclinical and Clinical Development of Anticancer Pharmaceuticals

WEDNESDAY | 10:30 AM
Preclinical Safety Evaluation of Oligonucleotide-based Therapies

WEDNESDAY | 1:30 PM
GLP and GCP: Perspectives from US and China

WEDNESDAY | 3:30 PM
Update and Experience with ICH M3R2

THURSDAY | 8:30 AM
Qualifying New Translational Safety Biomarkers for Nonclinical and Early Clinical Development

THURSDAY | 10:30 AM
GLP Study Sponsors, Monitors, and Contract Research Organizations

NHP – Natural Health Products

MONDAY | 10:30 AM
Good Manufacturing Practices for Dietary Supplements

MONDAY | 1:30 PM
New Dimensions in NHP Regulations

MONDAY | 3:30 PM
How FDA Reviews Botanical Drugs: Experience and Updates

TUESDAY | 8:00 AM
Safety Perspectives Including Adulteration for Dietary Supplements

TUESDAY | 10:00 AM
NIH Research and Development in Botanicals including Dietary Supplements

TUESDAY | 2:00 PM
Turning Wine Into Medication: Moving Natural Dietary Ingredients Into the Drug Route

OS – Outsourcing

MONDAY | 10:30 AM
Multiregional Clinical Trials: It Takes a Global Village of Expertise

MONDAY | 1:30 PM
Strategies for Successful Relationships Between Sponsors and CROs

MONDAY | 3:30 PM
Electronic Data Capture and Clinical Outsourcing

TUESDAY | 10:00 AM
Interactive eProcurement: An Innovative Technology Solution for CROs and Sponsors

TUESDAY | 2:00 PM
The State of Clinical Outsourcing

TUESDAY | 4:00 PM
Proven Methods for Reducing Change Orders and Accurately Assessing Their Impact

WEDNESDAY | 8:30 AM
It's Not Just a Project, It's a Relationship: The Site's Perspective

WEDNESDAY | 10:30 AM
Risks and Opportunities in the Emerging Markets, with a Focus on India

WEDNESDAY | 1:30 PM
Strategic Partnerships

Moving from a Fully Integrated Pharmaceutical Company to a Fully Integrated Pharmaceutical Network

WEDNESDAY | 3:30 PM
Resource Management in a Virtual Model: Effective and Efficient Spending

THURSDAY | 8:30 AM
Clinical Trials in the Fast Lane: Is There a Speed Limit on the Road to Excellence?

THURSDAY | 10:30 AM
Managing Strategic Partnering Relationships in R&D

PD/TR – Professional Development/ Training

MONDAY | 10:30 AM
The International Challenge and Enhanced Communications Through Cultural Understanding

MONDAY | 1:30 PM
Social Learning in a Regulated Environment: Can It Work?

MONDAY | 3:30 PM
Training: One Size Doesn't Fit All

TUESDAY | 8:00 AM
Coaching Teams in the Matrix Environment

TUESDAY | 10:00 AM
Effective Multicultural Clinical Staff Training: Embracing the Differences

TUESDAY | 2:00 PM
Learning, Survival, Success, and Career Development

TUESDAY | 4:00 PM
How to Use Web 2.0 in Training Programs

WEDNESDAY | 8:30 AM
An Overview of Drug Development for Emerging Professionals

WEDNESDAY | 10:30 AM
Pediatric Drug Safety

WEDNESDAY | 1:30 PM
A Career Survival Primer: Using Networks to Thrive Professionally

WEDNESDAY | 3:30 PM
Training and Education of Pharmaceutical Physicians

THURSDAY | 8:30 AM
Help Your Trainers Become Internal Training Consultants

THURSDAY | 10:30 AM
Cultural Awareness in a Global Workplace

PM/FI – Project Management/ Finance

MONDAY | 10:30 AM
Multiregional Clinical Trials: It Takes a Global Village of Expertise

MONDAY | 1:30 PM
Managing, Developing Business Relationships and Enhancing Partnerships

Earn Continuing Education Credits for tutorials and sessions. Visit www.diahome.org/annualmeeting for details.

How to Leverage Key Drivers in Portfolio and Project Management

MONDAY | 3:30 PM
Comparative Effectiveness Considerations in Venture Capital Funding Decisions

Implementing Earned Value Management in Clinical Operations

Right People, Right Place, Right Time: The Holy Grail of a Resource-constrained Industry

TUESDAY | 8:00 AM
Implications of Comparative Effectiveness Research for Health Care Innovation

The Project Manager's Role in Leading Successful Transitions in the Drug Development Cycle

TUESDAY | 10:00 AM
Evolving Demands in a Changing Industry: Are You Prepared?

TUESDAY | 2:00 PM
Effective Project Team Management: Dealing With Diversity Within Asia

Conflict Resolution: How to Manage Conflict on Alliance Teams

Project Termination: The Good, the Sad, and the Plan

TUESDAY | 4:00 PM
The Role of the Project Manager in the Implementation of Quality by Design

Adapting Project Risk Mitigation and Prevention Tools in Real-life Trials

WEDNESDAY | 8:30 AM
Addressing the Biopharmaceutical Industry's Leadership Challenges

Applying Critical Chain in the Life Science Industry

WEDNESDAY | 10:30 AM
Using Web 2.0 Technologies to Enhance PMO Effectiveness

The Changing Drug Development Environment: Effect on the Biopharmaceutical Project Manager

Financial Accruals for Clinical Trials: Basic Concepts and Effective Accrual Models

WEDNESDAY | 1:30 PM
The Role and Importance of Decision Analytics in Project and Portfolio Management

Crossing International and Functional Boundaries Project Management System in a Global Clinical Research Organization

WEDNESDAY | 3:30 PM
What Makes a Project Manager Effective?

Six Sigma in Drug Development: The Good, the Bad, and the Ugly Experiences in Deployment

THURSDAY | 8:30 AM
Effective Pharmaceutical Project Management Team Leadership

Seven Steps to Project Performance Metrics That Matter

THURSDAY | 10:30 AM
Marriage Counseling for the Project Team

PP – Public Policy

MONDAY | 10:30 AM
Clinical Trials on Trial: Potential Legal Liability Arising from Clinical Trials

MONDAY | 1:30 PM
Civil and Regulatory Liability from Clinical Trials

MONDAY | 3:30 PM
Drug Counterfeiting: New Actions and Initiatives

Legal Considerations for REMS Design and Implementation

TUESDAY | 10:00 AM
Mock Trial on Pharmaceutical Company Fraud and Abuse Settlements

TUESDAY | 2:00 PM
Drug Product Liability in the United States and the European Union

TUESDAY | 4:00 PM
Implications of Health Care Reform for Product Safety and the Pharmaceutical Industry

WEDNESDAY | 8:30 AM
Transparency of Clinical Trials

WEDNESDAY | 10:30 AM
Off-label Drug Use on Both Sides of the Atlantic

WEDNESDAY | 1:30 PM
Risk Managing Your Clinical Trial Process Against Liability Claims

WEDNESDAY | 3:30 PM
Influences of the Changing Drug Development Environment

THURSDAY | 8:30 AM
Incentives, Disincentives, and Market Powers: New Medicines for the World

THURSDAY | 10:30 AM
Building an Effective Compliance Program in Health Care Products R&D

RA – Regulatory Affairs

MONDAY | 10:30 AM
International Cooperation Among Regulators, Including the Exchange of Confidential Information

Combination Products

Consideration of Ethnic Differences in Global Drug Development ICH E5 Implementation

Qualification of Patient-reported Outcome (PRO) Tools to Support Labeling Claims: Development, Evaluation, and a Consortium Approach

Regulatory Roundtable on BioSimilar Policies

MONDAY | 1:30 PM
Going for BRIC: Accessing Emerging Markets and Japan Before or After US and EU Registration

Implementing a Life Cycle Management Regulatory Program for Therapeutics in Canada

CDRH Task Force Reports: 510(k) Devices Process Review and New Science in Regulatory Decision Making

Current Perspectives on the FDA Advisory Committee Process

MONDAY | 3:30 PM
Postmarketing Requirements and Commitments (PMRs/PMCs)

China's State Food and Drug Administration Update

FDA and European Medicines Agency Update on Relative Efficacy/Effectiveness

TUESDAY | 10:00 AM
Recent Reformation of Regulatory Agencies in the Asian Pacific Region

Comparative Effectiveness Research: Where Is it Headed in the US?

Critical Path Update

European Medicines Agency Town Hall

TUESDAY | 2:00 PM
Current Challenges in Development of Novel Vaccines

Regulatory Data Protection

PMDA (Pharmaceuticals and Medical Devices Agency) Town Meeting

FDA and European Medicines Agency Update on Pediatric Legislation

TUESDAY | 4:00 PM
CDER Compliance Update: Effective Enforcement Strategies

Global Pediatric Drug Development: All about Communication

Outlook for Changes in the Japanese Regulatory and Clinical Development Environment

High-impact Regulations and Guidelines in Canada, EU, Japan, and US

WEDNESDAY | 8:30 AM
Behind the Curtain with a Multinational Pharmaceutical Company for Pediatric Drug Development

Evolution of Risk Evaluation and Mitigation Strategies (REMS)

GRMPs and 21st Century Review Process

FDAAA Required Safety Labeling

WEDNESDAY | 10:30 AM
Acceptability of Foreign Clinical Data for Registration of New Medicines

Visit www.diahome.org/annualmeetingsessions for up-to-date information.

RA – Regulatory Affairs continued

WEDNESDAY | 10:30 AM
The Principles of Good Review Management Practices and Risk Evaluation and Mitigation Strategies (REMS)

Negotiating Regulatory Hurdles in Vaccine and Adjuvant Development and Licensure

Modernizing Regulatory Pathways in Personalized Medicine

WEDNESDAY | 1:30 PM
Clinical Trial Environment in the EU: Time for Changes

Behind the Curtain With the Pediatric Review Committee

PDUFA Reauthorization: Where Do We Go from Here?

Regulatory Harmonization and Cooperation Initiatives

WEDNESDAY | 3:30 PM
Regulatory Implications of the Final Rules for Expanded Access

21st Century Genomics Reviews at the US FDA

CBER Town Meeting

Marketed Unapproved Drugs Initiative, Formulary Management Decisions, and Corporate Responsibility

THURSDAY | 8:30 AM
CDER Town Meeting, Part 1 of 2

Update on Orphan Drugs in the US, EU, and Japan

THURSDAY | 10:30 AM
CDER Town Meeting, Part 2 of 2

Regulating Advanced Therapies

RD – R&D Strategy

MONDAY | 10:30 AM
Risks and Benefits in Using a Regional Service Providers (RPS) Model when Conducting Global Programs

MONDAY | 1:30 PM
Improving and Changing R&D Organizations with a Knowledge Management Focus

MONDAY | 3:30 PM
Impact of US and EU Pediatric Legislation

TUESDAY | 10:00 AM
Strategies for Drug Development in Oncology

TUESDAY | 2:00 PM
The Path Toward Mini-clinis: An Innovative Approach to R&D Effectiveness

TUESDAY | 4:00 PM
Pharmaceutical Patent Valuation: Novel Models and Applications in Industry

WEDNESDAY | 8:30 AM
Global Market Access and Reimbursement Strategies

WEDNESDAY | 10:30 AM
Personalized Medicine: Are We There Yet?

ST – Statistics

MONDAY | 10:30 AM
Multiregional Clinical Trials: It Takes a Global Village of Expertise

MONDAY | 1:30 PM
Noninferiority Studies: Regulatory and Industry Perspectives

MONDAY | 3:30 PM
Issues with Missing Data in Confirmatory Clinical Trials: Europe and US Views

TUESDAY | 8:00 AM
Meta-analysis Related to Regulatory Issues

TUESDAY | 10:00 AM
Making Room at the Health Care Policy Table: The Role of Statisticians

TUESDAY | 2:00 PM
Adaptive Design Clinical Trials – Part 1 of 2: Practical Experiences from Case Studies

TUESDAY | 4:00 PM
Adaptive Design Clinical Trials – Part 2 of 2: Guidance for Industry

WEDNESDAY | 8:30 AM
Modeling and Simulation in Clinical Development: Beyond Trial Design and Exploratory Analyses

WEDNESDAY | 10:30 AM
Design and Inference in Multiregional Clinical Trials

WEDNESDAY | 1:30 PM
Roles of Biomarkers or Genomic Biomarkers in Clinical Trials

WEDNESDAY | 3:30 PM
Randomization Issues in Multicenter Trials

THURSDAY | 8:30 AM
CDISC Update for Statisticians

THURSDAY | 10:30 AM
Collaborative Environments for Statistical Methodology Development

VA – Validation

MONDAY | 1:30 PM
Will Electronic Health Records (EHR) Destroy Clinical Research or Transform It?

TUESDAY | 10:00 AM
Optimizing Quality Management and Controlling Cost Using a Global Delivery Model

TUESDAY | 2:00 PM
Computerized Systems Used in Clinical Research: Best Practices from PEACH

TUESDAY | 4:00 PM
Using Agile Practices on Validated Solutions

WEDNESDAY | 8:30 AM
EDC, Clinical Studies, and Cloud Computing

WEDNESDAY | 1:30 PM
Validation Challenge of eClinical When EHR/EMR Is Integrated

WEDNESDAY | 3:30 PM
Clinical Software Validation in the Cloud (SaaS)

THURSDAY | 8:30 AM
An International Perspective on the Use of Computerized Systems

THURSDAY | 10:30 AM
Managing Validation Life Cycle Sans Paper: A Working Model

REGISTRATION FEES

Member Standard	$1290
Nonmember Standard	$1430
Charitable Nonprofit/ Academia Member	$815
Charitable Nonprofit/ Academia Nonmember	$955
Member Government	$420
Nonmember Government	$560
One-day Member	$765
One-day Nonmember	$905

Preconference Tutorials, Sunday, June 13

Pre-registration required.

- Understanding and Navigating the Regulatory System in China
- Structured Product Labeling: Content of Labeling and Drug Establishment Registration and Drug Listing
- Fourteen Steps from Research to Development
- FDA Enforcement: Understanding the Agency's Authority, How Violations Occur, How to Prevent Them, and How to Respond If Violations Do Occur
- Utilizing Chemistry, Manufacturing, and Controls in Drug Development
- Portfolio Management: The Nuts and Bolts of Aligning Operations with Strategy
- Early Clinical Studies: An Overview
- Developing Standard Operating Procedures (SOPs)
- Regulatory Affairs in the European Union: An Overview of Registration Procedures for Medicinal Products in the EU
- Leadership: How to Organize and Lead People in Group Work
- Japan Regulatory Environment: Overview of the Organization, Processes, Systems, and Changes Affecting Pharmaceutical Development
- Hot Topics in Pharmacovigilance in the EU: Eudra-Vigilance Access Policy, International Standardization Work E2B and Identification of Medicinal Products, Signal Detection, Duplicate Management
- A Device Primer: 510(k)s, PMAs, IDEs
- Designing, Operating, and Evaluating Patient Registries
- Social Media Marketing Accelerator
- Advanced CRO-vendor Management: Quality, Performance, and Compliance
- Regulatory Affairs for Biologics
- How to Prepare for a Safety Inspection
- Clinical Statistics for Nonstatisticians
- Who's Monitoring the Monitor: Explore Trends, Management Techniques and a Reality Check for Sponsors Utilizing CRO- and Alliance-based Site Monitoring

In Other Regions

Conferences

MAY 7-9, 2010
3rd Annual Regulatory Conference on "Global Regulatory Challenges: Quest for Optimization
INDIA

MAY 16-19, 2010
2nd DIA China Annual Meeting
Beijing, CHINA

Webinars

APRIL 20, 2010
10:00-11:30 AM EDT
Safety Reporting Requirements in Clinical Trials: Indian and European Perspectives

APRIL 22, 2010
11:00 AM–12:30 PM EDT
Update on AMCP Format Version 3.0: Industry Perspective

APRIL 29, 2010
12:00-1:30 PM EDT
CDER Town Meeting: Current Hot Topics Regarding eSubmissions

MAY 14, 2010
1:30-3:00 PM EDT
Discussion of FDA's Draft Non-Inferiority Guidance

MAY 20, 2010
11:00 AM to 12:30 PM EDT
FDA Discusses Signaling Using Data Mining Results

MAY 26, 2010
11:00 AM - 12:00 PM EDT
Guidance for Industry on the Contents of a Complete Submission for the Evaluation of Proprietary Names

Online eLearning

MEDICAL COMMUNICATIONS eLEARNING CERTIFICATE PROGRAM

CLINICAL INVESTIGATOR eLEARNING PROGRAM

INFORMED CONSENT MODULE

Online Training Series

MAY 3-14, 2010
12:00 PM – 1:30 PM DST
Basics of an IND - 6 Part Online

MAY 11-13, 2010
11:30 AM – 2:00 PM DST
Overview of Drug Development from Discovery through Marketing Application - 3-Part Online Training Series

MAY 17-26, 2010
12:00 PM – 1:15 PM DST
Basics of the NDA - Six-Part Online

JUNE 2-3, 2010
12:00 PM - 1:00 PM DST
Interactions with FDA during the IND/NDA Phases - Two-Part Online Series

JUNE 4, 2010
12:00 PM – 1:30 PM DST
Regulatory Aspects of Prescription Drug/Biologics Advertising and Promotional Labeling On-line Training Course

JULY 12-20, 2010
12:00 PM – 1:30 PM DST
Clinical Statistics for Nonstatisticians - 5-Part Online Training Series

JULY 19-27, 2010
11:30 AM – 1:00 PM DST
Computer Systems Validation for the Non-computer Professional Online Training Series

JULY 21-29, 2010
12:00 PM – 1:30 PM DST
Introduction to Signal Detection and Data Mining

AUGUST 9-17, 2010
12:00 PM – 1:00 PM DST
Fundamentals of Project Management for the Nonproject Manager - 4-Part Online Training Series

SEPTEMBER 16-30, 2010
10:00 AM – 12:00 PM DST
Development of a Clinical Study Report - 3-Part On-line Training Series

EudraVigilance

Electronic Reporting of ICSRs in the EEA
MAY 3-5, 2010
(MADRID, SPAIN)
MAY 17-19, 2010
MAY 26-28, 2010
JUNE 9-11, 2010
JUNE 14-16, 2010
JUNE 28-30, 2010
(SAN MARINO)
JULY 5-7, 2010
SEPTEMBER 1-3, 2010
SEPTEMBER 15-17, 2010
SEPTEMBER 20-22, 2010
(PARIS, FRANCE)

JUNE 22, 2010
8th EudraVigilance Information Day
London, UK

Medicinal Product Dictionary (EVMPD)

MAY 25, 2010
SEPTEMBER 14, 2010

IT MegaTrack

Monday, June 14, 1:30-3:00 PM

Will Electronic Health Records (EHR) Destroy Clin

This year's IT Mega Track will deal with the effect of electronic health records on clinical research. Now in its third year, the mega track format promotes broader discussion and consequently, deeper understanding of these essential topics. In addition to presenting the perspectives from regulatory agencies, this session will offer a panel of international experts to exchange views.

Session chairperson, J. Michael Fitzmaurice, PhD, FACMI, (Senior Science Advisor for Information Technology, Office of the Director Agency for Healthcare Research and Quality, United States), and David Fritsche, MBA (Vice President, Global BMRA IT and BMO Systems, Biomedical Operations, Genzyme Corporation, United States), who serves as chair of the IT track and was instrumental in developing this session, answered a few questions for the *Global Forum.*

Dr. Michael Fitzmaurice

Q&A We often focus on their beneficial impact on clinical operations, but what if any benefits do electronic health records provide to regulatory review and approval?

Since widespread adoption has yet to occur, although EHR adoption is expected to jump in the next five years due to ARRA incentive payments, we have to discuss the potential to support and demonstrate improvements in regulatory science—the science behind health care regulations. Some of these improvements are postmarketing surveillance of the safety and effectiveness of approved drugs and devices. EHRs would facilitate rapid determination of who is taking a drug that has been proven to have unfortunate effects or help identify who has an implanted device that has a higher-than-expected failure rate and provide an essential component in the development of a knowledge base of beneficial and detrimental effects of regulated products after they have been approved for use. Looking ahead, it is possible that, with the help of EHRs, a regulatory agency could approve a medical product contingent on the continued good results as revealed by a scientific examination over time of a cohort of patients who use that product.

Q&A How can EHRs benefit patient populations in emerging nations whose technological infrastructure may not be as advanced?

Having a patient's information from previous visits to the provider may be the start, in the absence of the ability to exchange the patient's information with other providers. Such information as medication lists, problem lists, followed by recent lab tests and perhaps images, could provide more informed decision making.

If this information is maintained in a standard format in each provider's EHR, it would enable valuable exchanges when the technology infrastructure advances. Information obtained outside the provider's office, such as laboratory tests, could be received in a common electronic format, with infrastructure advances.

nical Research, or Transform It?

An EHR's ability to print out the patient's information and the provider's willingness to give it to the patient will support greater patient involvement in his or her own care.

Q&A What can "industry" do to address patient concerns about data privacy and security issues in the EHR environment?

In the past 10 years, a stronger legal infrastructure has been developed that provides greater and greater protection for the confidentiality and security of a patient's health information.

Meaningful use of incentive payments will lead to a wider use of EHRs having these protections built in, including the ability for a provider to know where a patient's information has been accessed or disclosed, and by whom and to whom, respectively.

David Fritsche, MBA

Q&A Why were electronic health records chosen as the topic for this collaborative session?

Many of the abstracts submitted for the 2010 Annual Meeting mentioned EHR in one way or another. EHR was sometimes cited as a solution, sometimes as an opportunity, and sometimes as a problem. It was also obvious from the variety of the submissions that EHR has the potential to touch many aspects of our business.

Program Committee members discussed the situation at length, and determined the best way forward to bring greater clarity to the situation – assemble a panel of experts for a moderated discussion. Recognizing its potentially broad appeal across multiple tracks, the miniplenary idea was conceived and scheduled to permit maximum participation.

Q&A Are EHRs bridging across, or blowing up, the gaps between functional departments in clinical research?

The answer depends on your perspective. While beneficial to one set of processes in the health care setting, EHRs can be viewed as disruptive to other sets of clinical research processes. But like many disruptive technologies, once new processes are modeled that can take advantage of the technology, the improvements and benefits become apparent.

We are situated in the middle of this transition, with significant forces pushing for greater use of EHR and greater sharing of information across systems, but that is challenging to some current processes. For example, our clinical research methods rely on strict data handling and verification methods that have not yet been able to navigate the change. In the long run, EHR will help to bridge the information-sharing gaps, yielding potentially greater coordination of patient care information. ■

Interactive Regulatory Agency Sessions

The 46th Annual Meeting will host a variety of interactive regulatory sessions, from the classic CDER Town Meeting to new sessions featuring agency speakers and panelists from CDRH and CBER. For more details on these and other sessions, go to www.diahome.org and click on the Annual Meeting.

CBER

New for 2010, the CBER Town Meeting will take place on Wednesday, June 16 at 3:30PM. Robert A. Yetter, PhD (Associate Director for Review Management, Office of the Director, CBER) will serve as session chair. The session will provide an overview of CBER's current work on ongoing initiatives, guidances, and regulations.

CDER Compliance Update

Chaired by Deborah Autor, JD (Director, Office of Compliance, FDA), this session provides a venue for a focused discussion on effective enforcement strategies specific to drug products. The session is designed to promote feedback and input from the audience on current, proposed or newly implemented enforcement strategies —what works best and how to improve the enforcement process. This new, interactive session will be held on Tuesday, June 15 at 4:00PM.

CDER

The two-part CDER Town Meeting is always a highlight of the Annual Meeting. Chaired by Nancy Smith, PhD (former Director, Office of Training and Communications, CDER); the senior leadership team of CDER has been invited to participate in this session. Topics to be discussed will depend on the audience and on what areas are of current importance to the CDER community. Parts 1 and 2 will take place on Thursday, June 17 at 8:30 and 10:30AM, respectively.

"It was valuable for the industry to hear, first-hand, the FDA's thoughts on certain topics, as well as for the FDA to learn what is on the collective 'minds' of the industry."

"I learned a lot about timely issues related to regulatory filing, the review process, and new infrastructures such as FDAAA and REMS."

CDRH

"CDRH Task Force Reports: 510(k) Devices Process Review and New Science in Regulatory Decision Making" will be presented for the first time on Monday, June 14 at 1:30PM. This session will provide the opportunity for top-line components of two individual task force (launched in fall 2009) reports to be shared with attendees. Jonathan Sackner-Bernstein, MD (Associate Center Director, Post Marketing Operations, OCD, CDRH), will serve as session chair.

European Medicines Agency

Back for its second year, the European Medicines Agency Town Hall will be held on Tuesday, June 15 at 10:00AM. Anthony Humphreys (Head of Regulatory, Procedural and Committee Support, European Medicines Agency) will serve as session chair. The European Medicines Agency has developed initiatives and entry points to facilitate regulatory procedures and scientific dialogue from early development to postmarketing authorization stages. This session offers the opportunity to interact directly with a panel of European Medicines Agency staff.

"All panel members were excellent and provided very good answers and advice."

"Excellent session; excellent format."

PMDA Town Meeting

Returning again to the Annual Meeting, the PMDA Town Meeting will be chaired this year by Kyoichi Tadano (Director, Division of Planning and Coordination, PMDA) This session, presented on Tuesday, June 15 at 2:00PM, is always extremely well attended and offers the opportunity to interact directly with a panel of PMDA senior staff representing almost all services within the agency, including reviews/consultations, postmarketing safety measures, GCP/GMP inspections, international programs, future scientific issues, and procedural and regulatory issues. After brief introductory presentations, the majority of the session offers the audience the opportunity to pose questions to the panel. ■

"It is very useful to find out how PMDA plans to improve overall time to approval for new drugs."

Questions may be submitted in advance for the town meetings to 2010program@diahome.org with the appropriate subject line, eg, "Questions for CDER Town Meeting."

Executive Panel to Examine Industry & CME

The drive toward transparency and disclosure in the biopharmaceutical and medical device industries has come about through many converging circumstances and purposes. The issue of industry-provider interactions, including industry relationships with external constituents in the biopharmaceutical and medical device marketplace – in particular, academic institutions such as hospitals and medical schools – has moved to the center of attention not only for industry and academic leadership but for the public and policy makers. For example, this past September, *The Wall Street Journal* reported that a multinational pharma company planned to begin capping and publicly disclosing payments the company made to doctors; this same company also planned to stop financially supporting medical education programs from commercial providers and to fund only independent medical education programs offered by academic medical centers.

In 2007, the US Institute of Medicine (IOM) appointed a new Committee on Conflict of Interest in Medical Research, Education, and Practice to study industry financial support of medical education and training; to consider if such financial support could be construed to have undue influence on the professional practice of researchers, physicians, and other medical professionals; and to develop recommendations to identify, limit, and manage such conflicts, yet, at the same time, foster productive collaborative relationships between industry and the larger medical community.

Among the recommendations of this IOM report, issued in April 2009: That Congress create a national program for biopharmaceutical and medical device companies to publically report payments made to researchers and research institutions, physicians and other health care providers, and continuing medical education providers; and that academic medical centers and other research institutes prohibit individuals from conducting research if they have a significant financial interest in an existing or potential product or company that could be impacted by the results of that research.

IOM committee member Eric G. Campbell, PhD, Associate Professor at the Institute for Health Policy and Department of Medicine at Massachusetts General Hospital and Harvard Medical School, appeared before the Special US Senate Committee on Aging in July 2009 to discuss this report. "It is critical for public trust that research institutions protect the integrity of the medical research that is the foundation of clinical practice and education," said Dr. Campbell. "Although the committee did not reach agreement on a specific path to reform of continuing medical education, it concluded that the current system of funding is unacceptable and should not continue."

At this year's Annual Meeting, Dr. Campbell will serve as panelist

Arthur L. Caplan

on the first of two executive policy forum sessions, **The New Landscape for Industry-profession Relations: From Policy to Practice,** on Tuesday June 15. The first session, at 10:00AM, will feature discussion of the current public policy landscape among thought leaders from government, media, ethics, and academia, and will be chaired by Arthur L. Caplan, PhD, Emmanuel & Robert Hart Director, Center for Bioethics and Professor of Bioethics, University of Pennsylvania.

The second session, at 2:00PM, will examine strategies intended to restore and maintain public confidence in clinical research and medical education that are emerging from industry, medical societies, clinical researchers, and health care providers. This second session will be chaired by Minnie Baylor-Henry, Regulatory & Capital Markets Consulting, Deloitte and Touche, who joined DIA Executive Director Paul Pomerantz to share these thoughts about DIA's first annual meeting executive policy forum.

Q&A Why was this topic chosen for the first ever DIA Annual Meeting Executive Policy Forum session?

MBH: Given the criticality of the ethical issues that surround the interaction between the pharmaceutical and device industries and providers, in particular, the topic is so timely that it's in DIA's best interest, given DIA's important role in our industry, to provide the forum for this important discussion. It's a discussion that, within the pharmaceutical and device industries, is 'top of mind' for executives. Considering all the Sunshine Act issues and legislative issues in the states, plus new policies that are being enacted within the pharmaceutical and device industries and within medical centers, this topic is something that many, many of our members are interested in. We almost have an obligation to provide this forum.

PP: There's a broad public awareness of these relationships and some of the issues in those relationships between industry and providers and academia. Relative to DIA's mission, we're trying to provide a forum to open up discussion, and that's what DIA does so well –provide an opportunity for people to discuss potential issues and try to find common ground through these forums.

Q&A What different perspectives will the forum panelists present?

MBH: The first session will survey the landscape, look at the external environment from a policy perspective and get opinions from thought leaders from government, ethics, media and academia, who are working to drive policy initiatives and positions regarding the ethical issues that the industry and providers face in today's environment. The selection of our panelists – a medical ethicist, a director of research, and a continuing medical education executive – is consistent with the purpose of this panel. The first panel will look at the policy issues that people are facing.

The second panel will look at solutions and strategies from the industry, medical society, and researcher perspectives, and ask the question, 'How can the pharmaceutical and medical device industries, and academic health centers

Minnie Baylor-Henry

and health care providers, restore the public confidence that's so critical to changing the perception that's out there right now about what's going on in these relationships?' The panelists for this second session feature representatives from industry, a medical society, research, and an academic medical center, as well as someone quite familiar with the Washington (DC) environment and the issues that many in our industry face as a result of the dynamic issues that float around Washington.

The underlying issue is bias in clinical research findings, and transparency around these relationships.

PP: These issues have been described in the *Wall Street Journal, New York Times, The New England Journal of Medicine,* and *Health Affairs.* The issues relate to the impact of industry on the research setting, on medical education, on medical journals, and ultimately physician decision making. Industry has traditionally recruited physicians for advisory councils, to serve on boards, as thought leaders to teach and help promote the use of certain drugs or devices, and that has resulted in concern that decision making is being influenced more by industry direction than by science and concern over patient benefit. There are a lot of layers to this issue because it not only involves several different activities but a whole range of different types of products and devices involving many different specialties, including: orthopedics, oncology, cardiology, and neurosurgery. ■

Project Management in

Changing Contexts

Plenary Session, Tuesday, June 15, 10:00 AM

How hard is it to hit a moving target? Just ask a project manager currently working in the US biopharmaceutical or a related industry. These professionals must keep up with scientific and technological progress, navigate codes of international and federal regulations, manage strict budgets and schedules, and ultimately deliver safe and efficacious products to a marketplace that seems to grow both bigger (through globalization) and smaller (through the Internet and communications technology).

This year's Annual Meeting features a special Project Management/Finance plenary session at 10:00 AM on Tuesday June 15. **Evolving Demands in a Changing Industry: Are You Prepared?** will help attendees anticipate and overcome the unique business, scientific, and regulatory challenges that project managers in the biopharmaceutical and medical device industries face daily. This plenary session will feature panelists J. Carmel Egan, PhD (Eli Lilly & Company) and Kenneth I. Kaitin, PhD (Tufts University School of Medicine), and be chaired by Raymond G. Starrett, MS (Targacept, Inc.).

"One of the realities that we face in project management is that our business is changing all the time. The context of drug development as a whole has been fairly similar over the years, although a lot of specific aspects change as a result of regulatory evolution and that sort of thing. But from the standpoint of the pressure on our industry to deliver good drugs as efficiently as possible to meet patient needs, there's an overlying pressure on the industry to perform better than it has," Ray explains. "We have dismal metrics as an industry if we really look at it honestly."

"Within this plenary, we're going to talk through what the performance of the industry looks like in the context of today's world, and hopefully be able to 'tease out' some of the places where project managers can 'up their game' and have more of an impact on solving some of these problems," he concludes. Ray shared additional points of view on project management, and the industry context around it, in the following Q&A.

"One of the realities that we face in my discipline, project management, is that our business is changing all the time. The context of drug development as a whole has been fairly similar over the years, although many specific aspects continue to evolve as a result of regulatory

Raymond G. Starrett, MSc

evolution, scientific learning, and market dynamics. But from the standpoint of delivering good drugs as efficiently as possible to meet patient needs, there's an overlying pressure on the industry to perform better than it has. We have dismal metrics as an industry if we really look at it honestly. Within this plenary, we're going to talk through what the performance of the industry looks like in the context of today's world, and hopefully be able to 'tease out' some of the ways where project managers can 'up their game' and have more of an impact on solving some of these problems (eg, through better decision making, risk management, improved planning, and execution)."

Q&A In what ways has the FDA Amendments Act (FDAAA) of 2007 impacted the daily activities of biopharmaceutical and medical device industry project management professionals?

If you think about risk management as a part of project management, activities associated with the development and implementation of a REMS (Risk Evaluation & Mitigation Strategy) might involve earlier and more integrated planning. In the past, folks often reacted to things that may have come up during review of a submission (or post-market); now, they have to think about these issues and activities and their cross-functional implications earlier. This applies to the commercial as well as R&D implications.

Q&A What are three characteristics of an effective project manager?

A lot of other things play into this, but I believe there are three very important legs on this stool. One is actually developing, employing, and improving the skills and tool kit of applied project management. There can be somewhat of an artistic aspect, in terms of how people apply these skills and the style they use to apply them, but critical applied project management is a discipline with certain kinds of processes and tools and training necessary to implement it effectively. It's important to have the technical training in applied project management to understand how to develop and manage all of the aspects of integrated planning, resource management, and risk management, all the while staying aligned with portfolio strategies and priorities. The technical discipline of applied project management is critical.

Second, it's very difficult to imagine someone being an effective project manager in our business if they don't understand the context of what they're doing. Specifically, I'm talking about a broad knowledge about drug development processes and how all of the moving parts integrate with each other. This does not

J. Carmel Egan, PhD

mean having all-encompassing expertise in multiple functional disciplines – no one would be expected to have that – but to be effective in this role, you have to understand the nuances of drug development, which comes largely through experience. This explains why most people end up in project management roles after having some experience working in drug development, most often coming out of another discipline: If you were to poll most project managers, they would say that they worked in other drug development disciplines before they entered project management. It's very difficult to properly apply the project management skill sets without understanding your context and what you're trying to do in drug development. That's the second leg.

Third is the leadership component, an approach that is conducive to bringing teams together, working through problems, and effectively resolving conflict, the ability to manage stakeholders both upward and downward in organizations, and basically being able to inspire a team to achieve their best. Those would be the three most important legs upon which that stool stands.

Kenneth I. Kaitin, PhD

How can a project manager develop leadership skills – Isn't leadership something that a person either intrinsically has or has not?

This topic could absorb a hundred books and advanced degrees but my opinion is that leadership skills are something that people can learn. I do think it probably comes easier to some people than to others, but I'm not sure I agree that people are either born with it or they're not. There are a lot of leadership aspects that people can learn through training, practice, and feedback, and a good project manager is going to learn those skills or they won't be effective in the role. For a project manager/project leader in a matrix organization, often we have to lead without the apparent authority. I don't think that everybody who ends up in project management necessarily has that coming in, but they have to learn or they won't be successful.

Are certain project management skills more effective in early drug discovery stages while others are more effective in late development or postmarketing phases, or are the same general project management skills effective through all phases?

The toolbox, the skill set – the three legs of the stool that we mentioned – are applicable across the whole spectrum. But there's clearly a different focus at different stages of drug development: As you go through the early phases, you make a lot of decisions about direction, and the later stages are very much about execution, not that there aren't strategic implications or issues to resolve. You always have to deal with interactions with regulatory agencies, for example, and how to interpret them and potentially modify project plans as a result. I see an evolution of focus from strategic planning and decision making – even project selection, if you want to look at it from a portfolio level – into execution as you're looking at later stages. The skill set is the same, but you're applying it in a different context.

What advice would you give an undergraduate or graduate student who is considering pursuing a project management career in the biopharmaceutical or medical device industries?

Pay close attention to what you're interested in and seek a good mentor who is a PM practitioner. They need to basically be excellent within whatever discipline that they are entering, and try to find the opportunity that allows them to do that within the context of drug development. The earlier someone can get into the environment of drug development, the faster they'll pick up that one leg of the stool. ■

To find the complete list of **Project Management/Finance** Annual Meeting sessions, refer to the insert in this issue of the *Global Forum*.

It Takes a (Global) Village

Clinical Research MegaTrack Plenary

From beginning to end, as the drug development continuum moves through research phases, it traverses a systematic network of professional and scientific disciplines. Conducting clinical research in several different regions of the world simultaneously seems to expand this network into an entire universe of therapeutic, geographic, scientific, and regulatory considerations. How can you adequately represent these different phases, perspectives, and responsibilities in a single, comprehensive clinical development program plan?

Multiregional clinical trials are much more than just expanding your local trial to other sites around the world. This year's Annual Meeting features the Clinical Research megatrack plenary session **Multiregional Clinical Trials: It Takes a Global Village of Expertise** on Monday, June 14 at 10:30 AM. This multidisciplinary, multiregional plenary will examine practical experiences in the design, implementation, summarization, and registration of information on multiregional clinical trials, and the points at which they're all interconnected. Bruce Binkowitz, PhD, MSc (Merck & Co., Inc.), who will serve as plenary chair, and Douglas J. Peddicord, PhD (Association of Clinical Research Organizations), one of the plenary speakers, previewed this session and these topics in the following *Global Forum* Q&A.

Q&A It seems clear why and how regional regulatory considerations are different, but why and how do regional ethical considerations change in the context of global clinical trials?

BB: The regional ethical considerations do not change in the context of global clinical trials. They are of the utmost importance for all trials, global or regional. What changes for a global trial as opposed to a trial conducted in just a single region is that the cross-section of ethical considerations must be considered simultaneously in the planning and conduct of the trial.

DP: I fully agree: Ethical considerations and requirements within a region do not change when a trial is conducted globally – that is, across regions. Given the bedrock requirement of protecting the rights and welfare of research participants, local/national/regional requirements must always be observed; for example, in India not only the institutional ethics committee but the ICMR (Indian Council of Medical Research), working on behalf of the DCG (Drugs Controller General), typically provides

Bruce Binkowitz

ethical and scientific review of research protocols. General ethical principles, such as the requirement for fully informed consent, apply universally; other ethical considerations, such as whether a placebo arm is to be included in a trial, may vary across regions. In a global trial, the challenge, then, is to ensure that local/national/regional requirements are met, while maintaining a level of ethical standards in the conduct of the trial that protects the rights and welfare of all research participants around the world.

Q&A Do multinational clinical trials employ different patient recruitment and retention strategies in different regions, or are the same strategies and practices generally used across every region in the trial?

BB: Ideally, a single protocol multinational trial would employ the same recruitment and retention strategies because standardization of processes within a multinational trial leads to better ability to generalize the results, and in addition, more opportunity to reduce any "noise" introduced into the trial by these different strategies. In reality, there are can be cultural and social differences that influence how patients are recruited into multinational trials. These differences also can differ across the patient population being treated.

DP: Certainly, the inclusion/exclusion criteria for a given trial will be the same across regions, and I would agree that standardization of all processes, including recruitment and retention strategies, is ideal. However, while trial recruitment and retention are predicated a great deal on the interaction between investigator and participant regardless of location, cultural differences are highly relevant to recruitment and retention. From the content of advertising to the language used in the informed consent process, it is incumbent on sponsors and investigators to present information in culturally relevant and meaningful ways. This challenge applies to any trial, whether conducted in a single region or globally.

Q&A What is "drug pooling" in clinical trials, and what are its benefits and limitations?

BB: Pooling of drugs for a clinical trial involves the use of a common inventory that is shared across multiple studies. The supplies are held at a central location(s), usually not labeled, or at the investigator sites where they have been labeled. The drugs will be used for multiple studies. This is not an issue particular to multinational trials. It is an issue particular to drugs needed for multiple studies, and an efficient way of holding a pool of these drugs and allocating them out to the various studies in need of these in a real-time manner so that drug supplies aren't stored at each investigator site, which can be potentially wasteful of drug supply

Douglas J. Peddicord

if recruitment at a site does not go as anticipated. The benefits would be in efficiency of drug supply and cost. Interactive Voice Response systems are often used to handle drug pooling strategies, as manual tracking can be complicated.

Q&A What are adaptive clinical trial designs and how are they changing traditional phase 1-phase 4 clinical research?

BB: An adaptive design is a clinical trial design that uses accumulating data in a clinical trial to alter design features of the trial while it is in progress. The rules of the adaptation(s) must be spelled out ahead of the trial – for example, in the protocol. Adaptive designs can improve the quality and quantity of information from clinical trials while maintaining or reducing numbers of patients and/or study duration. In some cases a single adaptive clinical trial can replace two or more traditionally designed clinical trials. ■

To find the complete list of **Clinical Research** sessions, refer to the insert inside this issue of the *Global Forum*.

Advertising, Marketing & MedComm MegaTrack Plenary on CME

The topic of Continuing Medical Education (CME) will be discussed throughout the upcoming 46th Annual Meeting, including the two-part Executive Policy Forum on **The New Landscape for Industry-profession Relations: From Policy to Practice** that convenes at 10:00 AM and 2:00 PM on Tuesday June 15 (see related article on page 57).

Over the past several years, various initiatives by public and private institutions have addressed different aspects of CME, including: Proposals from the Institute of Medicine (IOM) and the Association of American Medical Colleges (AAMC) on funding for drug prescribers' CME; from the Accreditation Council for Continuing Medical Education (ACCME) on commercial support of CME; and from such medical societies as the American College of Cardiology (ACC), American Medical Association (AMA), and the Council of Medical Specialty Societies (CMSS), to restrict commercial involvement in CME; plus new and forthcoming transparency legislation at both the federal and state levels. Potential bias that might be introduced into CME content, based upon who pays for the development and dissemination of that content, has consistently been at the forefront of these initiatives.

CME also provides the topic for the joint Advertising, Marketing, and Medical Communications MegaTrack plenary session at 10:30 AM on Monday June 14. **Is Industry-supported Education the Next Taboo?** will examine how company compliance, marketing, and education/training departments, are responding to these events and the challenges they present. This session will be chaired by John F. Kamp, JD, PhD (Coalition for Healthcare Communication), who shared his thoughts on this topic in the following *Global Forum* Q&A.

Q&A Why was industry-supported CME chosen as the topic for this megatrack plenary session?

JK: Despite all the regulation of CME, the industry and commercial providers of CME have taken hits in policy circles for the past several years. Consider the major report from the Senate Finance Committee in 1997, a nasty hearing before the Senate Aging Committee in 2009, an IOM report calling for major changes, academic medical centers refusing commercial support, etc. Following the Washington maxim, "no good deed goes unpunished," the Macy Foundation and the AAMC have called for an end of commercial support for CME. In the meantime, major companies including Lilly, Pfizer, and GSK, have decreased their commercial support over the past few years and instituted "reforms" limiting content, speakers, and providers.

Q&A What are some of the alternatives being discussed to replace industry financial support of CME?

JK: Virtually no one has come up with a realistic idea to replace the decreasing dollars for commercial support. More importantly, virtually no one has come up with a sustainable model to replace this support.

Q&A Why should "the average American" who might typically fill one or two prescriptions per month be concerned about how CME is financed and by whom?

JK: Doctors and other health care providers learn about new drugs and new uses of existing drugs largely from CME, including that supported by drug companies. Accrediting groups, including ACCME, AMA and the American Association of Family Physicians (AAFP), have strict guidelines on these activities, the FDA and HHS have issued guidances that are carefully followed, and doctors do not report "bias" in these programs. Why fix a system that is not broken? ■

John F. Kamp

To find the complete list of **Advertising**, **Marketing**, or **Medical Communications** sessions, refer to the insert inside this issue of the *Global Forum*.

MONACO 2010

Images from DIA's 22nd Annual EuroMeeting

Opening Plenary

Welcome to the 22nd EuroMeeting

DIA's President, Executive Director, European Director, and the program co-chairs welcomed attendees to the 22nd EuroMeeting at the opening plenary session in the Grimaldi Forum, surrounded by the beautiful landscape of Monaco.

Director, DIA Europe, Brigitte Franke-Bray opened this plenary by thanking all volunteers who contributed to the EuroMeeting program, with special thanks to the DIA staff in the European office for all their efforts and the European Pharmacy Student Association and the International Federation of Medical Student Associations for their participation. "I would like to thank EURODIS, the voice of rare diseases in Europe, and its CEO, Yann Le Cam, and also Ariane Weinman. Here in Monaco we celebrate the fifth anniversary of our collaboration with EURODIS and the patient fellowship program," said Brigitte. "I also want to give a very big 'thank you' to the delegates of the patient organizations who will speak at this event. We all very much hope that you will be able to see and appreciate the work that has gone into preparing and presenting this excellent scientific program."

"The more time I spend at DIA, the more I recognize that DIA's strength is our volunteers, and how the collaboration we see among our elected leaders, volunteers, and staff, helps DIA realize our

goals," said Executive Director Paul Pomerantz. "I am very impressed by this innovative meeting, which not only includes professionals from many disciplines but many students and young professionals, our future health industry leaders, and patient organization representatives, our partners in innovation and the primary purpose for why we do what we do."

Welcoming remarks by Board of Directors President Jeffrey Sherman, PhD, FACP (Horizon Therapeutics), continued this collaborative theme. "For me, the dynamics of what we do also reinforces just how integral it is for all of us to work together, from our volunteers to our dedicated staff to our board members to our advisory councils, and, most importantly, to all of you," he said. "I ask all of you here today to consider this: What will be your role in shaping the DIA of the future?"

EuroMeeting co-chairs Kirsten Franzen, M Pharm Sci (Pfizer, Sweden) and Professor Bruno Flamion, MD, PhD (University of Namur, Belgium; Chair, CHMP, Scientific Advice Working Party, European Medicines Agency) focused their welcoming remarks on the program content. "When first drawing up the outline of the program, we wanted to reflect activities and trends in the present environment, things that we deal with on an everyday basis," said Kirsten. "We have chosen to drift away from the 'share experience' paradigm and go for more of a debate on current issues and hopefully also push these debates forward."

"I am an MD and have never been a member of a medicines agency or a pharmaceutical company," Bruno explained. "If you are a patient yourself, you know how intensely hopeful one can be about new drugs, new approaches that will make your condition easier to stand, and your life happier to live. So my hope, when accepting to co-chair this meeting, was to help DIA build their annual platform where people can think together, get new ideas, and realize that we have to work more closely together to overcome the upcoming crisis in therapeutics around the world."

The business portion of the EuroMeeting opening plenary session also included presentation of the DIA Volunteer Service Awards; please see the related article on page 70. ■

DIA Continues its "GREENEST EXHIBITOR" Award in Monaco

The winner of the 2010 EuroMeeting Greenest Exhibitor award was CRF Health. Accepting the award are (left), Andy Lewis, Project Manager, and (right) Kai Langel, Senior Systems Specialist.

The 2010 EuroMeeting was in the forefront of the "green" meetings trend, using practical, innovative, and often simple measures to reduce its carbon footprint and practice the 3Rs: reduce, recycle, and reuse.

The first Greenest Exhibitor award was given in 2009, and it was very well received by the exhibitors. The award recognizes the exhibitor who does the most to green their booth, for example, packing lightly when shipping and offering to email brochures rather than providing paper copies.

The 2010 award was presented on Tuesday, March 9 at 1:30 PM at the DIA booth.

Paul Pomerantz, DIA's Executive Director, and Jeff Sherman, DIA President, presented the award to Andy Lewis and Kai Langel, who accepted on behalf of CRF Health, which also won the award in 2009. CRF Health's "green" efforts include offsetting their travel miles through CarbonFund.org, a paperless booth, and environmentally friendly giveaways. ■

Poster Winners Recognized at EuroMeeting

Brigitte Franke-Bray (left) and Jeff Sherman (right) with the student poster winners, from the left, Niyazi Oztoprak, Viola Galligioni, and Joao Eduardo Duarte.

Student Posters

The DIA booth was the site of the Student Poster Award ceremony, which took place on Tuesday, March 9 at 5:30PM. Students submitted posters addressing topics similar to those in the EuroMeeting programme. Accepted student poster abstracts were published in the March issue of the *Drug Information Journal* (volume 44, number 2, pages 199-204).

At the award ceremony, DIA President, Jeff Sherman, spoke about the importance of students to the association. He and Brigitte Franke-Bray, Director, DIA Europe, presented the awards.

The prize winners are as follows:

1ST Prize of €1000
João Eduardo Duarte, Faculty of Pharmacy, University of Lisbon, Portugal
New Approach on the Development of an Anti-VEGF Drug Delivery System

2ND Prize of €500
Niyazi Oztoprak, Cambridge University, UK
Capturing the Value of Information in Pharmaceutical R&D

3RD Prize of €300
Viola Galligioni, University of Bologna, Italy
Nose-to-Brain Delivery of 1-(beta-D-ribofuranosil) -1, 2, 4-Triazole-3-carboxamide (Ribavirin, RBV) for the Treatment of Viral Encephalitis

Watch www.diahome.org for details of the student abstract process for Geneva 2011.

Professional Posters

Ten professional posters were on display in the Foyer on Level 2 of the Grimaldi Forum. The poster review committee selected a winning poster, and the prize, a DIA clock, was presented on Wednesday, March 8 during the lunch break. The ceremony was held at the DIA booth, and Brigitte Franke-Bray and Paul Pomerantz presented the award.

The professional poster winner is:
Barry Mulchrone, Quintiles, Ireland
A Review of Additional Risk Minimisation Measures for Products Approved via the EU Centralised Procedure since November 2005 ■

The professional poster deadline for the 23rd EuroMeeting in Geneva will be early January 2011. Monitor **www.diahome.org** for details.

The winning professional poster is carefully scrutinized.

Award Winners at the EuroMeeting

DIA's service awards recognize significant individual or group accomplishments in the discovery, development, regulation, surveillance, or marketing of pharmaceuticals or related products, and/or recognize significant volunteer contribution in the advancement of the DIA mission, vision, and values.

On Monday, March 8, DIA recognized the outstanding contributions of three distinguished volunteers during the opening plenary session of the 22nd Annual EuroMeeting in Monaco.

Distinguished Career Award- Per Helboe

The Distinguished Career Award recognizes and honors an individual with a distinguished career in the discovery, development, regulation, surveillance, or marketing of pharmaceuticals or related products. The recipient of this award has shown extraordinary service and dedication to the advancement of healthcare through career contributions to pharmaceutical and related industries that benefit industry, government and the patient.

Per Helboe

Per Helboe is the senior director of the Licensing Division of the Danish Medicines Agency. He graduated as a pharmacist in 1968 from the University of Pharmaceutical Sciences, Copenhagen. He completed his PhD in 1973 and defended his doctoral thesis (DSc) in 1989. He was appointed professor at the University of Copenhagen, Faculty of Pharmaceutical Sciences, in 2009.

Prof. Helboe has been affiliated with the Danish Medicines Agency over a lifetime. His early research interests focused on analytical pharmaceutical chemistry. His research focus developed over the years to more managerial and leadership roles within medicines registration in the international context.

Prof. Helboe has been actively involved in setting the standards in the EU on requirements to the quality part of dossiers for marketing authorization. He was a member of the CHMP Quality Working Party from its founding in 1985 until 2001 and functioned as chair from 1993 to 1995. In recent years, Prof. Helboe has been involved in several working groups on issues related to digitalization

of the licensing procedures in the EU.

Prof. Helboe was active in the ICH harmonization process during a period of 10 years, from the beginning in 1991 until 2001. He served as an EU representative on quality issues. From 1995 to 2001, he functioned as the EU ICH Coordinator for Quality.

Prof. Helboe worked with the European Pharmacopoeia for more than 20 years. He functioned as Vice Chair of the Commission from 1992 to 1995. Prof. Helboe was one of the founding fathers of the so-called Certificate of Suitability procedure which was established in 1992. He chaired the Technical Advisory group of the procedure from 1994 to 1997.

Recently, Prof. Helboe was instrumental in formalizing the official cooperation between Denmark (DMA) and China (SFDA). Denmark is one of the first countries in the EU to enter such agreements with China, which manufactures medicines and active ingredients at a faster pace than for example the western countries – and where consumption is growing rapidly.

Prof. Helboe was a member of the DIA European Steering Committee from 1993 to 1998, He has been active in DIA events as chair and speaker on many occasions.

Excellence in Volunteer Leadership Award-Fergus Sweeney

This award is given to recognize the individual who has demonstrated outstanding effective leadership during their dedicated and extensive voluntary service to the DIA. For 10 years or more, this individual has made consistent and significant contributions to the Association, not only as a volunteer, but as a volunteer-leader in various DIA roles. Some of these roles should include leadership positions in the following areas: meetings / workshops, communities, special committee positions, advisory council, editorial board, author or DIA board membership. The breadth and depth of their service as a leader to DIA should have a lasting, positive effect in contributing to the fulfillment of the mission and vision of the association.

Fergus Sweeney

Fergus Sweeney is Head of the Compliance and Inspection Sector at the European Medicines Agency. He joined the European Medicines Agency in 1999 to coordinate GCP and more recently pharmacovigilance inspection-related activities. He was appointed Head of Sector for Compliance and Inspection in May 2009.

Fergus has been an active contributor to DIA activities since the early 1990s. He has presented and chaired sessions on a wide range of GCP-related topics, development of quality systems for clinical research, computer system validation, laboratory systems, clinical trial registries and transparency, and regulatory aspects of clinical trials. Fergus is a longstanding faculty member and now course director for the DIA GCP Audit and Inspection training course.

Fergus received a Degree in Physiology in 1979 from Trinity College, Dublin, Ireland, a Doctorat de Troisiéme Cycle from the Université de Paris, France, in 1982, and a PhD in Pharmacology from University College Dublin, Ireland in 1986. Prior to joining the European Medicines Agency he worked in industry, in CROs, from 1982 to 1999 covering Phase I-IV clinical research, pharmacovigilance and laboratory activities, primarily in the field of quality assurance audit. He has carried out audits of investigator sites, laboratories, and sponsor/CRO sites in many countries across Europe, Asia-Pacific, and North America.

The European Medicines Agency Compliance and Inspection sector is responsible for the coordination of GCP, GLP, GMP/GDP and Pharmacovigilance inspections carried out in support of the centralized procedure. The sector provides the secretariat, coordination, and chairs for the European Inspectors' Working Groups. The sector provides the secretariat for the Quality Working Party, coordinates sampling and testing of centrally authorized products, and issues Certificates of Medicinal Products for the Agency. The sector manages the GMP annexes of Mutual Recognition Agreements and coordination of inspection activities with its counterparts in third countries and international organizations. The business analysis and coordination for the EudraCT and EudraGMP database systems are key sector activities.

Founders Service Award-Yves Juillet

The Founders Service Award is named after the group of 30 professionals who founded the DIA in 1964 with a fundamental value that the Association is member driven and fueled by the pharmaceutical industry's need for a neutral forum.

Yves Juillet

Having previously received the Outstanding Service Award, this next award level would be given with the highest recognition and appreciation for volunteerism in the DIA organization. It recognizes those individuals who have contributed to the advancement of the mission, vision and values of the DIA and fostered its growth and development through their dedicated and sustained volunteerism.

Yves Juillet is currently Senior Advisor to Leem (the Pharmaceutical Industry Association in France). He received his MD in 1975 from the University of Paris. He is board qualified in Cardiology, Intensive Care, Internal Medicine, and Pharmacology (MSc). He was Head of a Clinical Department at Broussais Hospital in Paris and Assistant in Pharmacology at the Medical University of Paris.

Yves joined SNIP (now Leem) in 1982 as Scientific Director before becoming Deputy Director General in 1987. He joined Roussel Uclaf in 1991 as Inspector General. He became Director of Pharmaceutical and Public Affairs of Hoechst Marion Roussel in 1995 and in 1999 Director of Public Affairs of Aventis Pharma.

He was the Chairman of the EFPIA Scientific Technical and Regulatory Policy Committee (1991-2002). He was a member of the ICH Steering Committee from 1996 to 2006, where he represented the European pharmaceutical industry and was the Chair of the Global Cooperation Group (ICH – rest of the world).

He has chaired the IFPMA (International Federation of Pharmaceutical Industries and Associations) Regulatory Policy Committee since 2004. He is a Member of the Academy of Pharmacy and a correspondent Member of the Academy of Medicine of France.

Yves has been involved in DIA activities since 1990. He chaired several tracks and sessions at Annual and European DIA meetings and gave numerous presentations dealing with regulatory, clinical and public policy issues. He was a member of the Annual Meeting Program Committee in 1994, 1998 and 1999, and of the EuroMeeting Program Committee in 2000 and 2003-2006 He chaired the EuroMeeting Program Committee in 2004. In 1998, he received a DIA Outstanding Service Award. He was a Member of the DIA Board of Directors from 2002 to 2008 and is currently a member of the DIA Advisory Committee for Europe. Yves chaired a session at the 2010 EuroMeeting.

Outstanding Service Award-Monica Pietrek

The DIA Outstanding Service Award is given to recognize those individuals who consistently, through their volunteer efforts, have made contributions to the DIA mission and vision over the past several years. These individuals have exceeded expectations in their volunteer activities with DIA.

Dr. Monika M. Pietrek is a medical doctor and epidemiologist. Having worked in clinical care, pharmaceutical, and CRO industries and at a regulatory agency, she has a broad-based experience in international health care with specific expertise in clinical development, drug safety, and risk management. In addition, Dr. Pietrek has gained substantial knowledge in process design/analysis and quality management.

Dr. Monika M. Pietrek

During the past 20 years she has held senior positions at Behringwerke, the Paul-Ehrlich-Institute, Hoffmann-La Roche, and PRA International, managing staff and projects across continents. Since 2009, Dr. Pietrek and colleagues provide their services to the pharmaceutical, biotechnology, and medical device industry through Pietrek Associates GmbH, an independent consultancy firm.

Dr. Pietrek has served as DIA volunteer for more than 15 years, as a speaker, session chair, theme leader, and as a member of various program committees for the annual conferences and workshops in North America and Europe, the Continuing Medical Education Committee, and the Regional Advisory Council of Europe. At present, she is co-chair of the Professional Education, Training and Development SIAC and a member of the Editorial Board of the *Drug Information Journal,* as well as the program committee of the Clinical Forum 2010. ■

2nd DIA China Annual Meeting

Priming China for Drug Innovation and Development

The 2nd DIA China Annual Meeting will be held from May 16-19 in Beijing, China. The Annual Meeting is again co-sponsored by the China Center for Pharmaceutical International Exchange (CCPIE) under China's State and Food Drug Administration (SFDA). The theme of the meeting is *Priming China for Drug Innovation and Development: From Strategy to Execution*.

This multidisciplinary meeting will serve as an international and neutral forum to discuss priming China as an emerging leader in executing drug development and will benefit all professionals from regulatory agencies and institutions, the biopharmaceutical industry, investigational sites, contract research organizations, and academia. Together we can better understand how to reach the next stage for our profession as well as deliver benefits for human health and well-being globally.

The conference will feature an opening session and half-day plenary presentations on May 17. Speakers from key regulatory agencies in China and other major countries will cover the general session topics below:

- Regulatory Affairs (4 sessions)
- Clinical Research (4 sessions)
- Pharmacovigilance (2 sessions)
- Clinical Data Management and Statistics (2 sessions)
- Nonclinical Safety Assessment (1 session)
- CMC/GMP (1 session)
- R&D and Biotechnology (2 sessions)

The Annual Meeting includes an exhibition during the main conference and will be preceded by several workshops on May 16. All events will take place in the Crowne Plaza Sun Palace in Beijing. ■

For further information please contact **Stephanie Liu** +86 10 5923 1109 or *dia@diachina.org*.

To Learn More, Plan to Attend this Annual Meeting Session

China's State Food and Drug Administration Update (Monday, 3:30-5:00 PM)

Chinese Pharmaceutical Association (CPA) and DIA Forge Memorandum of Understanding

Front: Prof. Wang Xiaoliang, CPA Vice President, Mr. Paul Pomerantz, DIA Worldwide Executive Director. Back (left-right): Mr. Wang Aiguo, CPA Director of Academic Department, Mr. Dai Gang, CPA Editing and Publishing Department, Ms. Li Shaoli, CPA Deputy President & Secretary General, Mr. Chen Bing, CPA Deputy Secretary, Mr. Yuan Tianxi, CPA Vice President, Mr. Liu Chunguang, CPA Director of International Affairs, Mr. Alfons Westgeest, DIA China, Mr. William Brassington, DIA Worldwide Director of Finance, Mr. Steven Basart, DIA China, Dr. Ling Su, Member of DIA Board of Directors and Chair of DIA's Advisory Council of China, Mr. James Cai, Member of DIA's Advisory Council of China (aTyr Pharma), and Ms. Maggie Ma, Member of DIA's Advisory Council of China (Covance).

DIA in China and the Chinese Pharmaceutical Association (CPA) announced their intention to collaborate on a joint newsletter and to develop educational opportunities and training for global and regional pharmaceutical and related professionals.

DIA and CPA signed a memorandum of understanding on February 25, 2010, which outlines plans to train professionals involved in the development, discovery, and life cycle management of pharmaceuticals and related products on a variety of topics including clinical trials, laws and regulations, drug safety evaluation, and quality control.

"DIA leadership remains committed to providing educational opportunities to professionals in emerging markets like China," says Paul Pomerantz, DIA Worldwide Executive Director. "The signing of this memorandum of understanding between DIA and the Chinese Pharmaceutical Association further solidifies this commitment and marks an important milestone in the continued growth of DIA in China."

Representatives in attendance from DIA and CPA included:

- Ms. Li Shaoli, CPA Deputy President and Secretary General
- Professor Wang Xiaoliang, CPA Vice President
- Mr. Yuan Tianxi, CPA Vice President
- Mr. Paul Pomerantz, DIA Worldwide Executive Director
- Mr. William Brassington, DIA Worldwide Director of Finance
- Dr. Ling Su, Member of DIA Board of Directors and Chair of DIA's Advisory Council of China

"DIA and the Chinese Pharmaceutical Association share the common goal of advancing pharmaceutical science in China," explains Dr. Ling Su." No doubt this collaboration will help to facilitate the development of safe and effective pharmaceutical products." ■

REPORT FROM DIA India

DIA's Provisional Advisory Council of India with Sultan Ghani, William Brassington, and Paul Pomerantz.

Nandkumar Chodankar and Sultan Ghani

Introduction

With its rapidly growing pharmaceutical and biotech industry, India has an accelerating need for a credible international forum that brings together individuals from industry, academia, and regulatory agencies to educate its drug development professionals and young entrepreneurs on the regulations, clinical practices, safety, and quality standards that will impact the approval of drugs developed in India for the global market.

There is a significant need to improve the health of the population by providing high-quality, safe, and effective drugs. In support of all these elements, there is a greater need for educational development programs for health professionals in various disciplines of the health sciences and health care technologies.

The DIA India office is situated at 303 Wellington Business Park, Marol, Mumbai. Besides its operational staff, DIA India is supported by a Provisional Advisory Council of India (ACI), which consists of 29 well known and respected professionals who provide guidance and strategic direction from a regional point of view to position DIA India to best serve its members.

Looking Forward

The year 2010 started with many positive activities. With the assistance of Dr. Stephen Wilson of the US FDA, DIA India organized a training workshop, **Clinical Trials and Design Analysis-US Regulatory Science Perspective**, at three different locations, Bangalore, Hyderabad, and Delhi, on January 10, 12, and 15, respectively. More than 100 participants attended the workshops, and excellent positive feedback was received from the participants.

- The new Advisory Council member Moin Don (J&J–India) worked with the ACI team and organized a very successful workshop on **Pharmacovigilance and Risk Management** in Chennai, India, as a part of the Tamil Nadu Chapter activities. This was attended by more than 100 participants, and DIA India received much positive feedback.

- The DIA Student Chapter of the Bombay College of Pharmacy organized a seminar at the SieTech Centre, where over 100 students participated from various pharma colleges in and around Mumbai. A number of students expressed their interest in joining DIA as student members.

- In February 2010, the DIA Worldwide Executive Director, Paul Pomerantz, visited India. Although his visit was short, he had a series of meetings both at Delhi and Mumbai. In Delhi, he met with a group of senior executives from the pharmaceutical industry and institutes. Later on, he met with government officials and officials from the FICCI. A highlight of his trip was a visit to the DCGI office, where he met with Dr. Surider Singh. DIA's new Vision and Mission, as well as cooperation between DIA and the Government of India and Ministry

of Health, were discussed. Paul also met with a few institute officials and discussed future cooperation and strategic alliances that DIA wants build in India.

- Paul's visit to Mumbai included a meeting with the US FDA (India), Country Director, and Dy. Country Director, as well as a visit to the DIA India Office and a meeting with the Provisional Advisory Council of India, where he outlined DIA's new Mission and Vision and participated in the council's discussions. Paul emphasized that he would like to see DIA move toward building and developing more strategic alliances. A dinner meeting was held at Mumbai with dignitaries from industry and government.

Future Events

- DIA is offering a course on **CTD Dossier Requirements: Focus on EU Module 1 and Quality Module 3** on March 21-22 at the SieTech Centre in Mumbai and on March 24-25 at the Taj Banjara in Hyderabad. This course will be given by two experts from European regulatory authorities and industry.
- The 3rd Annual Regulatory Conference, **Global Regulatory Challenges – Quest for Optimization,** is scheduled for May 7-9 in Mumbai. The conference will be co-chaired by Suhas Chaudhari Maharashtra (FDA), and Dr. Albinus M. D'Sa (Dy Country Director US FDA – India).
- DIA India has planned a workshop with WHO and EDQM on **Active Pharmaceutical Ingredients** in September 2010, in Mumbai.
- DIA is organizing the fifth Annual Conference on **Drug Discovery and Clinical Development** in Bangalore, in October 2010. The Program Committee is working actively on developing the program.
- Additional training programs on project management and regulatory affairs are planned during 2010 at different locations.
- Two new regional chapters are also planned for this year, one at Delhi and other at Hyderabad. ■

Nandkumar Chodankar, PhD, *serves on the DIA Board of Directors and as chairperson of the Advisory Council of India.*

Sultan S. Ghani *serves as Director of DIA India.*

Advisory Council of India

Chairperson	Padma V Devarajan	Syed Mubarak Naqvi
Nandkumar K Chodankar	Moin Don	Ranjani Nellore
Members	Antony Raj Gomes	Annabelle Rajaseharan
Amrita Bajaj	Hafeez Iqbal	Deepti Sanghavi
Kapil Bhargava	Vishwanath Mahesh Iyer	Balasubramanian Sankaranarayanan
Krathish Bopanna	Venkat Jasti	S.S. Sardessai
Suhas Chaudhari	Milind Joshi	Shirish Dattatraya Sherlekar
Louis Coutinho	Nandini K Kumar	Ajit Singh
Albinus M D'Sa	Vishwanath Malkar	Saranjit Singh
Sameer S Deb	Nigel Barrington McBean	Santanu K Tripathi
Rajiv Desai	Larisa Nagra Singh	Subramanian Ramaswamy Vaidya

To Learn More, Plan to Attend these Annual Meeting Sessions

- Pharmacovigilance in Asia: The Japan, China, and India Perspective (Tuesday, 2:00-3:30 PM)
- Conducting Clinical Trials in India and China: GCP Compliance and Maximizing Quality at Investigative Sites (Tuesday, 4:00-5:30 PM)
- Offshore, Re-shore or Right-shore: Risks and Opportunities in the Emerging Markets, with a Focus on India (Wednesday, 10:30 AM-12:00 PM)

13th Annual Workshop in Japan for CDM

Mr. Makoto Yokobori, Vice-Chair of the Program Committee (left) with Ms. Reiko Takada, Session Chair (middle) and Ms. Mineko Fujimoto, Program Committee Member (right).

Makoto Yokobori

The 13th Annual Workshop in Japan for Clinical Data Management was held on February 4-5, 2010 in Tokyo. There were approximately 270 attendees at the workshop from all over the world.

Attendees were interested in learning what the future held for CDM professionals. They posed a number of questions on these topics: How will medical industries change in the future? How will CDM continue to evolve? What will be required of CDM? What kinds of skills should professionals working in CDM acquire? The workshop tried to answer these questions. Its main theme was *CDMAA: CDM Amendments Act – The differences among "I know," "I understand," and "I can make it."* The theme included messages about how CDM should evolve and create its own future.

The workshop began with two keynote speeches. The first focused on the "Current Status of the Five-year Plan and Approaches for Global Studies" and was presented by Mr. Takeyuki Sato, Director, Office of Clinical Trial Promotion, Research and Development Division, Ministry of Health, Labour and Welfare (MHLW). Mr. Sato explained the clinical development environment in Japan and participation in global trials from the standpoint of the regulatory authority. Additionally, he presented a vision for the future. His presentation provided a high-level overview of pharmaceuticals in Japan.

The second keynote address was on the "Secondary Use of Data from Electronic Medical Records" and was presented by Dr. Michio Kimura, Director and Professor, Department of Medical informatics, Hamamatsu University School of Medicine. Dr. Kimura discussed a standard format for use with electronic medical records. He also spoke about his expectation that EDC will work more efficiently by using this format. This presentation provided the latest information for data capture.

The second day was organized as a multitrack. Hot topics such as new technology in EDC, updated CDISC information, and topics concerning future trends were presented in track A. Educational lectures concerning basic knowledge of biostatistics, CSV (Computerized System Validation), CDISC, MedDRA, and outsourcing were included in track B. This presented a good opportunity for beginner-level attendees.

Dr. Mitsune Yamaguchi, Deputy Director for GCP Inspection, Office of Conformity Audit, Pharmaceuticals and Medical Devices Agency (PMDA), presented "Conformity Audit of Clinical Trials Using EDC" at the end of track A. He took questions from the hall beforehand, as well as answering about 30 questions that were submitted by attendees. Recently, the use of EDC for data in NDAs has increased in Japan. Therefore, the comments on validation from the viewpoint of an auditor were very valuable for the attendees.

On the morning of the first day, a special program, the CCS (CDM Chatting Session) was held, with about 70 attendees. The young clinical data managers divided into eight groups and freely discussed issues they encounter in their daily work. The CCS has many supporters and many repeat attendees.

Planning has begun for the 14th Annual Workshop in Japan for CDM, currently scheduled for January 27–28, 2011. ■

To Learn More, Plan to Attend

PMDA (Pharmaceuticals and Medical Devices Agency) Town Meeting (Tuesday, 2:00-3:30 PM)

No Borders for Cardiac Safety – Japan To Implement the ICH-E14 Guidance

Boaz Mendzelevski

Cardiac safety of new drugs came to the public attention and became a regulatory focus following reports of sudden cardiac death associated with several drugs, most notably Terfenadine (antihistamine) and Cisapride (a gastrointestinal prokinetic). Both drugs were shown to be potent blockers of the rapid delayed rectifier potassium channel (Ikr), also known as the hERG (human ether-a-go-go-related gene) channel and can promote a life-threatening cardiac arrhythmia known as Torsade de Pointes (French for "twisting of the points"). With the growing body of knowledge, drug-induced cardiovascular toxicity became the primary reason for withdrawals and nonapprovals of new drugs.

The European regulators were the first to respond to these cardiac safety concerns with the CPMP's "Points to Consider" guidance document (CPMP/986/96), released in December 1997. This was followed by the Health Canada (HC, March 2001) and the combined HC and United States Food and Drug Administration (US FDA) "Preliminary Concept Paper," presented in November 2002. Shortly thereafter, in January 2003, the International Conference on Harmonization (ICH) adopted the HC/FDA concept paper for global implementation, as ICH topic E14. Both ICH topic S7B, the nonclinical guidance for assessment of drug induced proarrhythmia, and ICH-E14 were finalized in May 2005.

The ICH-E14 guidance calls for the majority of new drugs to undergo a thorough assessment of their effect on the QTc interval. At the center of the guidance is a single clinical pharmacology trial, the "Thorough QT/QTc (TQT) study," typically conducted in healthy volunteers. The study is designed and powered to detect a small mean change of up to 5 milliseconds (msec) in the QTc interval with a one-sided upper 95% confidence limit excluding as much as 10 msec baseline and placebo-adjusted QTc prolongation. The study design involves 2 doses of the investigational product (IP), the intended therapeutic dose and a supra-therapeutic dose, which is multiple-fold higher than the therapeutic dose, possibly the maximum tolerated dose (MTD), aimed to assess the worst-case scenario of drug exposure due to metabolic or physiologic factors. In addition, the study includes two control groups, placebo and a positive control. The latter is required to provide an assay validation for the entire study, demonstrating that any negative result (no QT prolongation of the IP) is a true negative and not a failure of the study design or conduct.

The stated regulatory objective of the TQT study is primarily to define the intensity of ECG monitoring during the late-stage development program. Consequently, the FDA now requires the TQT data prior to or at the end of the phase 2 meeting. Failure to present the TQT data at this regulatory milestone may result in regulatory penalties such as "clinical hold" or a requirement for an intensive ECG/QT monitoring during the late-stage studies until the TQT study results are available and demonstrate no cardiac safety risk.

The E14 guidance has first been introduced and implemented by the FDA and European EMEA. Japan, the third ICH country/region, has been

relatively late in implementing the E14 guidance. In October 2009 the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) released the long-awaited Japanese version of the E14 document. The new guideline will affect Japanese NDA submissions starting 1 November 2010. As with the US and EU versions, the Japanese ICH-E14 guidance is largely the same as its harmonized counterpart documents. Interestingly, the words "thorough QT study" are not used and instead, a "QT/QTc evaluation study" is used in the Japanese version.

One of the expected key differences in the implementation of the E14 guidance in Japan is that most TQT studies required for regulatory approvals of NDAs in Japan will still be conducted outside of Japan, primarily in the US and Europe, mostly involving caucasians. This raises the question of the need to extrapolate foreign TQT data into the Japanese NDA. However, unlike the better-known ethnic differences in drug metabolism and PK exposure, the extent and prevalence of ethnic differences in QT pharmacodynamics (PD) are not yet well established. The PMDA is therefore charged with judging, on a case-by-case basis, whether to require supporting data to enable extrapolation of drug-induced QT effects into Japanese subjects.

Finally, while the TQT study remains the centerpiece of the regulatory QT assessment paradigm, new initiatives to assess the predictive value of alternative approaches, including combining nonclinical data with intense QT assessment in early clinical studies, are being developed. All these and other topics will be discussed at the forthcoming 1st DIA Cardiac Safety Workshop in Japan, scheduled for May 25-26, 2010, in Tower Hall Funabori, Tokyo, Japan. ■

***Boaz Mendzelevski, MD**, is Vice President of Cardiology, Medifacts International, UK. He serves as program chairperson for the upcoming 1st DIA Cardiac Safety Workshop in Japan.*

To Learn More, Plan to Attend this Annual Meeting Session

Phase 1 Clinical Safety: Subjects and Signals (Tuesday, 10:00 -11:30 AM)

The Importance of Latin America in Global Clinical Trials: Expanding Clinical Research Beyond Borders

Marlene Llópiz Avilés

Over the past several years, biopharmaceutical and medical device companies have increased innovative R&D outside traditional boundaries and expanded clinical drug, biotechnological, and device development into many countries. This dramatic increase in globalization may be attributed to greater competition in the US and European markets, cost and patient recruitment challenges, and greater demand for qualified clinical research professionals. The rapid economic growth and improved regulatory processes in emerging and growing regions, partly driven by wider adoption of ICH guidelines and principles, are other important factors: Sponsors can find many opportunities to develop their products in "nontraditional regions" as part of their multinational strategy, and have the opportunity to market their drugs/devices elsewhere.

While the US, Canada, France, and the United Kingdom have experienced negative growth in clinical trial participation, Latin America has come into the limelight for pharmaceutical, biotechnological, and device studies. Countries such as Mexico, Argentina, and Brazil, have recorded substantial positive growth rates, along with India, Russia, and China.[1,2] (Figure 1) Over 80% of the Latin American market share of pharmaceutical sales and growth is distributed among Mexico, Argentina, and Brazil. However, biopharmaceutical companies are starting to uncover new opportunities in other Latin American countries such as Costa Rica, the Dominican Republic, Ecuador, Guatemala, Panama, and Venezuela.

A vastly populated, varied region with close to 569 million inhabitants[3], Latin America provides large drug-naïve patient populations with common and special disease profiles, rapid compliant patient recruitment, motivated and experienced investigators, and US- and EC-equivalent medical standards, as well as highly experienced monitoring and project management teams thoroughly trained on GCP and ICH guidelines. More than 6,500 clinical trials are currently being conducted throughout Latin America.[4] (Figure 2)

Partnering contract research organizations (CROs), regulatory businesses, patient recruitment companies, and government agencies have also paid closer attention to promoting and conducting international and global clinical trials in Latin America. The timely fashion and quality of regulatory compliance strategies related to their studies or those of their clients involve several easy-to-follow steps. Initially, all necessary documentation must be collected for translation into Portuguese for trials in Brazil and into Spanish for all other countries in the region. As in many other countries, clinical trials in Latin America require an institutional review board (IRB) at each site and Ministry of Health (MoH) submissions and approvals, which are executed under standardized international ICH/GCP guidelines and local regulations.

CRO regulatory affairs departments are often in charge of regulatory requirement compliance follow-through, outsourcing translations, document review and revision, ethics committee and MoH submissions, fulfilling label and trial material requirements, customs strategies and authorization processes for clinical trial supplies and materials import/export, drug storage supervision, distribution and destruction of expired or unused study drugs and supplies, pharmacovigilance reports, and product registration, marketing, and sales authorizations within each country.

Conducting studies in Latin America provides sponsors with an array of countries for testing drugs, reduced costs for strategic multicenter studies, credible and objective results for marketing approval submittals, and highly professional staff members at contract research organizations who are bilingual, graduated in allied health and medical fields, and trained and experienced in analyzing and monitoring clinical trials. One additional advantage to conducting clinical trials in Latin America is the assurance that trials will be conducted following international regulations. Health care systems in Latin America have changed substantially, research has become more proficient through improved operating standards, and regulations have become stricter and formally aligned with global regulatory and health authorities.

Important therapeutic indications seen in patients in Latin America include oncology, heart conditions, gastroenterology, neurology, orthopedics, hematology, HIV/AIDS, immunology, women´s health, endocrinology, respiratory ailments, urology, dermatology, and psychiatry. It has recently been determined that the leading causes of death in Latin America include heart disease, cancer, infectious diseases, and diabetes mellitus. Even though mortality rates from infectious diseases are declining, the regional incidence of cancer, chronic and lifestyle diseases, heart disease, stroke and diabetes are on the rise. According to the International Diabetes Federation, more than 6.8M adults in Mexico (over 10% of the adult population), and 7.6M adults in Brazil, have diabetes.

Vaccines and medical devices have also become new topics of interest.

One grave error that sponsors often make is using Latin American countries as "rescue countries" for trials. Because of the nature of patient recruitment, countries in this region should be considered in the initial stages of country selection and trial conduct instead. Start-ups in parallel with other countries for global trials play to the advantage of sponsors as patients are often recruited faster in Latin America.

After country selection – depending on the therapeutic indication, incidence and prevalence – select principal investigators and sites with the necessary experience and according to the study protocol and requirements. Steps to organize and submit required documentation include: Nondisclosure agreements signed upon the receipt of protocols (or synopses) and client requests for proposals; study budgets should be submitted to sponsors as soon as possible, dependent on country, sites, patients, complexity of trial, etc.; investigator and study site facility confidentiality agreements are signed; translation of documents into Spanish (and into Portuguese, for Brazil); powers of attorney are processed for the CRO to manage the trial; and submitting a letter describing the study to the EC along with the protocol, informed consent form, investigator´s brochure, patient diaries and case report forms (CRF).

Once EC approval is granted and a letter of authorization is obtained, submission is then done at MoH. Officially submit all study and site documents in English and Spanish. In certain countries, after obtaining approval from a local EC, documents must then be submitted to a national EC, either in sequence or in parallel. After MoH approval, solicit an import license, which provides the manufacturer´s and supplier´s name and address and a description and the quantity of the product, and contract with certified warehouses for study supply receipt and distribution to sites. In sum, regulatory submission and approvals vary per country, and may range from four to seven months.

In conclusion, large, urban patient populations in Latin America enable faster enrollment and easier patient follow-up. These populations often see clinical trials as viable health care options for gaining access to free medication and closely supervised and specific health care, which leads to high patient retention rates. Sites in LA allow for more patients per site to be enrolled, compared with North America and Europe, and have well trained investigators knowledgeable in GCP and ICH guidelines. Countries in this region have disease patterns that reflect both the West and the developing world, which allows for the study of different therapeutic indications. And, finally, the quality of data collected is comparable to that of data from any other country in the world. Latin America should be considered as a viable and convenient option for global clinical trial conduction from the "get go!" ■

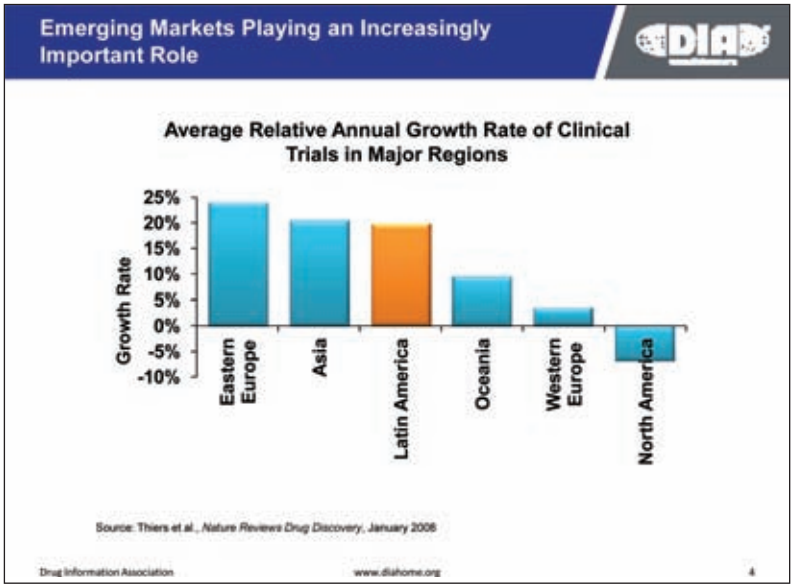


Figure 1

Country	Number of Clinical Trials
Central America	1297
Mexico	1128
Argentina	960
Bolivia	12
Brazil	1647
Chile	519
Colombia	332
Ecuador	51
Paraguay	6
Peru	452
Uruguay	28
Venezuela	94

Figure 2. Number of clinical trials conducted in Latin America

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DIA, FDA, & PhRMA Collaborate on M&S in Drug Development Conference

DIA collaborated with the FDA and the Pharmaceutical Research & Manufacturers of America (PhRMA) to present a conference that examined an increasingly important approach for improving the efficiency and success rates of drug development programs, **Modeling & Simulation in Drug Development: Quantitative Approaches for Decision Making**, in Bethesda, MD, on October 28–29, 2009.

One result of the FDA Critical Path Initiative is the earlier and increased application of modeling and simulation (M&S) tools – such as computer simulation, and mechanistic and stochastic modeling – beyond their traditional use by clinical statisticians and pharmacologists, into such areas as dose selection and regimen optimization during clinical study program design and planning. Rajesh Krishna, PhD, FCP (Merck & Company, Inc.), and José Pinheiro, PhD (Novartis Pharmaceuticals Corporation) served as conference co-chairpersons.

M&S scientists not only impact different industry functional areas but often come from different educational backgrounds. So, in addition to the traditional opening keynote address, this conference presented an introductory lecture designed to address similarities and differences across the respective "Taxonomy of Modeling and Simulation" that these professionals use. This lecture was delivered by Mats Karlsson, PhD, FCP (Uppsala University). The keynote address, "The Vision of Modeling & Simulation for Clinical Trials: FDA & Industry Perspectives," was jointly delivered by Robert O'Neill, PhD (CDER, FDA) and Donald R. Stanski, MD (Novartis).

Points in the drug development and review process where the agency sees the potential of M&S include exploratory development and dose finding; evaluation of a sponsor's proposed late-phase protocol, study design, and analysis plan during the IND phase; evaluation of a completed trial submitted during the NDA phase; and postapproval "what if" benefit/risk scenario assessments. Dr. Stanski presented, from the industry perspective, results of a recent PhRMA Model-based Drug Development Survey, which indicate that modeling groups are located in different parts of different organizations, and that modeling currently has more impact on late drug development phases, and less in early phases.

Modeling & Simulation in Early Development

Sessions began with an examination of gaps and opportunities in the use of strategic M&S in early clinical development. The first presentation summarized the PhRMA Adaptive Dose Ranging Studies Working Group's study of adaptive dose finding designs, conducted to demonstrate the belief that high attrition rates in many phase 3 studies are largely due to inadequate dose selection. For trials where safety is the primary consideration, adaptive designs that model safety as well as efficacy show promise for outperforming designs that model efficacy alone. Pharmacometrics in early drug development from the regulatory perspective included review of the FDA Guidance for Industry for End-of-Phase 2A (EOP2A) Meetings published in September 2009, which notes the importance of sponsor-regulator discussions about quantitative drug development methods (eg, trial simulation using disease, drug, placebo, and dropout models)

before initiating phase 2b and phase 3 studies. This presentation concluded that the future of successful EOP2A programs lies in powerful disease models, data/modeling standardization, and collaborative multidisciplinary work. FDA continues to collaborate with industry and other external resources to develop these models.

Modeling & Simulation to Inform Design & Analysis

Trial simulations almost always improve trial designs because the simulation process facilitates systematic scenario evaluations that enable better quantitative decisions. The next sessions illustrated the benefits and challenges of using M&S-based methods to design and analyze clinical studies for producing confirmatory evidence and labeling information. M&S tools can help evaluate properties of the design and analysis strategy for pivotal trials. These tools are also used for design and operational decisions in late-stage trials, and to explore sample size, enrollment rates, the timing of interim analyses, and the effect of drop outs or missing data, in such trials. M&S tools seem quite underused, however, in the interpretation and analysis of data from these trials.

From Early to Full Development: Strategy & Efficiency

The following session overviewed how M&S can help bridge the gap between early-phase trials and late-phase drug development, based in part on a case study of the role of M&S in a biomarker-based development program. Leveraging prior quantitative knowledge and M&S tools can justify clinical trial designs and enhance their efficiency. Furthermore, by creating frameworks that integrate multiple information sources, for example, M&S tools for decision analysis can reach beyond design of phase 2a trials to the overall product development program strategy.

Breakout Sessions

The first day of the conference ended with breakout sessions that provided participants the opportunity to interactively discuss three important subtopics, the results of which were shared in the next day's opening plenary session with the complete audience: *Missing Data; M&S in the Learn & Confirm Paradigm; and Model Development Using Accumulating Data: What About Model Validation?*

Modeling & Pharmacogenomics

Because traditional biostatistical methods alone cannot assess the clinical utility of a biomarker, clinical and genomic modeling during early- to late-phase clinical trials can determine the variability of treatment effects due to genomic or other factors, and the clinical utility of genomic biomarkers. Presentations in these sessions included an overview of the Microarray Quality Control (MAQC) Consortium, composed of more than 30 data analysis teams who are each developing numerous models for predicting outcomes in their respective fields of interest.

Product Differentiation

The conference perspective shifted to the impact of economics on the current drug discovery and development landscape, and emphasized modeling tools that can evaluate and predict product differentiation as a key component of pricing and reimbursement. Presentations also reviewed the Clinical Utility Index (CUI), which quantifies the tradeoffs that are often made among the effects comprising the product profile by providing a single metric for multiple dimensions of benefit and risk. In this context, the important question is not "*How much does this clinical trial cost?*" but "*How much is this clinical trial worth?*" in terms of the reduced disease burden for the patient, and the dollar value of the program for the developer.

Modeling Safety & Epidemiology

Participants further explored how CUI can inform quantitative pharmacology, as an example of drug safety assessment methodologies. CUI has utility for making necessary decisions both within (dose selection, comparative populations, regimens, or formulations, and study design) and between (differentiation with market leader, relative value in competitive market) compounds. Accurate definition of clinically meaningful parameters, and selection and weighting of attributes, are essential elements of these decisions. Discussions also included ways to model infrequent longitudinal adverse events and conditional sequential sampling approaches to adverse event monitoring.

M&S: Path Forward/Next Steps

The final session convened a panel discussion that reviewed ways to advance the understanding and appropriate use of M&S tools for both design and analysis of exploratory and confirmatory trials, and ways to collaboratively engage pharmacometricians, clinical pharmacologists, statisticians, and others who routinely use M&S tools within their specific disciplines, to help advance this understanding.

Early in 2010, the *Global Forum* posed several questions about current and future modeling and simulation topics to program co-chairs Rajesh Krishna, PhD, FCP and José Pinheiro, PhD.

Q&A What do you believe is the biggest misconception about the use of quantitative modeling & computer simulation tools in drug development programs?

One of the biggest misconceptions about this area lies with the value proposition. This discipline is still largely viewed as tactical and not strategic within clinical development. Consequently, these tools are restricted to supportive and exploratory analyses. M&S approaches are the basis of modern protocol development, and are widely used and accepted at the design stage of clinical studies. At the analysis stage, however, there is still some reluctance in relying on model-based results for primary analysis and, more broadly, decision making. Concerns about validity of assumptions, lack of experience and expertise, etc, may partly explain, but certainly do not justify, the reluctance in utilizing model-based primary analyses in clinical development. Moreover, the influence of such approaches in drug development and regulatory decision making is presently undervalued.

Q&A What benefits do modeling & simulation tools contribute to clinical trial designs, and how?

M&S offers a transparent, assumption-driven approach to design of clinical trials. Specifically, M&S allows the proper characterization and quantitative evaluation of the risk/benefit distribution associated with various development scenarios. These are key elements of informed, scientific decision making when comparing alternative design strategies, both at the study and program levels. In particular, M&S allows the investigation of the sensitivity of particular designs to underlying assumptions, such as variability in primary endpoint, potential informed drop-outs, and so on.

Q&A This conference featured breakout sessions on three separate but related topics; was there any unexpected or surprising feedback from these breakout sessions?

The scope of the discussions that occurred during the breakout sessions reflects in large part, the diversity of functional disciplines involved in M&S. Thus, it was increasingly clear that the view on a particular modeling approach was different depending upon what functional discipline was represented. That said, M&S facilitates integration of diverse scientific opinion, resulting in a consensus-based approach to decision making.

Q&A Many conference topics focused on drug development, but postapproval drug safety initiatives also continue to grow in importance; what can modeling & simulation tools contribute to pharmacovigilance and other postmarketing safety initiatives?

One of the main challenges of postmarketing safety initiatives will be to monitor and detect relevant signals in meaningful amounts of observational data (that is, data not obtained from a controlled clinical trial, but rather collected in actual medical practice through surveillance). Model-based approaches have the potential to provide a link between the postmarketing observational data and the program development clinical study data, helping focus on the most relevant safety issues. Modeling can also be used to leverage the association among safety endpoints (eg, adverse events from the same patient or same body system) to better sort out spurious events from relevant signals. The use of M&S in this area is still emerging, and best practices would need to be identified and promulgated.

Q&A As this topic continues to grow in importance, what do you envision will be "hot topics" at a similar modeling & simulation conference two or three years from now?

Looking forward, such topics will almost certainly include regulatory acceptance of model-based analysis in confirmatory trials, for both approval and labeling; model-based meta-analysis to characterize dose-response and safety signals, so that new drug candidates with optimal risk/benefit profiles are developed; use of Bayesian modeling as a tool for integrating knowledge across development programs, so that cross-program platform level learnings can be harnessed; safety signal detection with pre- and postmarketing data using M&S to provide informed assessment on risk; and continued exploration of case studies and best practices that highlight both the benefits and pitfalls of model-based drug development ■

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Applications of Modeling and Simulation in Cardiac Safety Studies

Giridhar S. Tirucherai

The role of modeling and simulation (M&S) in improving the efficiency of the drug development process is being increasingly realized in contemporary drug development. Modeling is a retrospective process that creates a mathematical and physiological model that best explains the observed data, while simulation is a prospective process that uses the mathematical and physiological model to predict what will be observed in future studies. M&S can be very informative in the context of the ICH E14 thorough QT/QTc (TQT) study, an important cardiac safety study. Some applications of Modeling and Simulation specific to thorough QT studies were discussed in the recent DIA webinar presentation titled "Cardiac Safety Issues in Early Drug Development." [1] These applications are summarized below.

1. Dose selection/justification

A key objective of thorough QT studies is to characterize the risk of QT prolongation under supratherapeutic exposures of the drug. Selecting a supratherapeutic dose can be a challenging task when the maximum tolerated dose has not been established in early clinical studies and a sponsor desires to perform a thorough QT study fairly early in drug development, ie, at a stage when some of the informative drug-drug interaction and/or special population studies have yet to be performed. The first case study demonstrated the utility of M&S in selecting a supratherapeutic dose for a TQT study.

Concentration-time data from various doses in a first-in-human study were modeled using a pharmacokinetic (PK) model. The PK model was then used to simulate the exposures that would be achieved if the therapeutic dose of the drug were to be administered to subjects having varying levels of inhibition in systemic clearance, consistent with mild, moderate, and severe impairment. The simulation showed that the proposed supratherapeutic dose would result in concentrations that would be considerably higher than those obtained when the therapeutic dose was administered to patients with mild, moderate, or severe impairment in clearance. M&S therefore supported a justification for the proposed supratherapeutic dose, even though studies characterizing the relative importance of metabolism and renal elimination were yet to be initiated in product development.

2. Interpreting the results of a thorough QT study

Several recent reports have shown that the intersection union test is associated with a notably high rate of false positives, ie, falsely concluding that there is a significant

This article and the one following it are based on presentations from DIA's Cardiac Safety Webinar, presented on October 21, 2009. In addition to the authors, Nenad Sarapa, MD (Head of Clinical Pharmacology-Oncology, Hoffmann-La Roche, United States) and Norman Stockbridge, MD, PhD (Director, Division of Cardiovascular and Renal Products, OND, CDER, FDA) made important contributions to the success of this webinar.

drug-related effect when the prolongation is in fact minimal.[2-3] It has been posited that an alternate approach, namely, concentration-QT modeling (aka "C-QT" modeling) has the advantage of being founded on the pharmacology of drug-induced QT prolongation,[3] and allows a more thorough understanding of the variability in baseline QT and C-QT response.[4] The second case study compared the C-QT modeling approach against the primary E14 analysis performed for a TQT study.

Two doses of a drug were evaluated in a four-treatment-arm parallel TQT study. The study was deemed "positive," per the E14 endpoint, with the maximum mean difference and the upper one-sided 95% CI between drug and placebo being 3.9 (7.6) ms and 9.3 (13.1) ms, for the therapeutic and supratherapeutic doses, respectively. An artificially inflated result was suspected upon close examination of the observed ECG data at steady state. The observed ECG values for placebo on steady state day were approximately 7 ms lower at all timepoints, relative to the values on baseline day (Day-1), indicating the possibility that the time-matched mean double-delta values were likely overestimated. All data (ie, baseline, treatment, and placebo) were subsequently modeled together using a nonlinear mixed effects approach. Observed QTc at a given timepoint was modeled as the sum of a mesor baseline parameter, plus the diurnal variability around that timepoint (expressed using multiple cosine functions), a placebo effect term to account for the downward drift in observed ECG values on steady state day, and a linear drug effect term to account for the drug-related increase in QTc. The full C-QT model estimated that the maximum mean drug-related increase in QTc was 0.8 (1.2) ms and 3.6 (5.2) ms, for the therapeutic and supratherapeutic doses, respectively. M&S showed that the estimates of QT prolongation using the C-QT approach were well under the regulatory specified threshold of concern, once the drift in observed ECG values on steady state day was appropriately accounted for.

3. Prediction of QTc effects for doses not evaluated in a TQT study

The last case study described the usefulness of a C-QT model to predict risk of QT prolongation at therapeutic doses from a TQT study that evaluated drug effect on QTc at doses that were mostly considered supratherapeutic.

Concentration-QT data were modeled using nonlinear mixed effects modeling. Since the drug had a significant effect of slowing the heart rate, the primary QTc correction (QTcI) used in the E14 analysis was considered inappropriate. The individualized heart rate correction factor, estimated using baseline data alone was deemed not to be representative of the drug-induced decrease in heart rate (ie, increased RR interval) following dosing. To overcome this difficulty, a one-stage concentration QT modeling approach was adopted, wherein separate correction factors were estimated for "on-drug" and "off-drug" data. Diurnal effects in QTc were modeled using cosinor functions, and a sigmoidal Emax delayed effect model was selected as the drug effect model. Mean estimates of QT prolongation at different doses obtained from the one-stage C-QT model were about 2 to 3 ms lower than those from the primary E14 analysis using QTcI, presumably due to over-correction of QTc at low heart rates. More importantly, the C-QT model predicted that the concentrations resulting from therapeutic doses that were originally not evaluated in the TQT study would have been associated with insignificant QTc effects. Thus, a more complete characterization of the drug's proarrhythmic potential was possible using M&S.

All three case studies demonstrate that M&S can play an important role in the design as well as analysis of data from TQT studies. It is highly recommended to incorporate the principles of M&S during all stages of drug development to maximize the probability of success and minimize time to market.

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Integrated Cardiac Safety Programs

Assessing Cardiac Safety throughout Clinical Development

J. Rick Turner

Introduction

Regulatory requirements for assessing the proarrhythmic liability of investigational noncardiac drugs are now widely acknowledged. One clinical trial of particular note is the ICH E14 Thorough QT/QTc (TQT) study.[1-4] This is dedicated to the meticulous evaluation of a drug's liability to delay myocardial repolarization and hence prolong the QT interval as seen on the surface electrocardiogram (ECG). However, the TQT study is best conceptualized as one component of an integrated cardiac safety program that incorporates nonclinical investigation and several additional clinical assessment strategies. This article focuses on the latter.

The TQT Study: A Very Brief Overview

To put subsequent discussions in context, the TQT study is reviewed very briefly here. The "traditional" study design employs four treatment arms:

- A positive control that is known to increase the QT/QTc interval (typically moxifloxacin) to establish assay sensitivity;
- A placebo control, against which the following two drug doses are compared;
- The proposed therapeutic dose of the drug;
- A supratherapeutic dose that is several multiples of the proposed therapeutic dose, intended to mimic what may happen should the drug be approved and prescribed for patients who have compromised metabolism or excretion and/or are taking other medications, each of which may lead to greater -than- intended concentrations of the drug in the body.

Results from the TQT study determine the extent to which ECG monitoring should take place in therapeutic confirmatory studies.

Complementary Assessment Strategies

Three important considerations in an integrated cardiac safety program are:

- At what point should the TQT study be conducted?
- How should the supratherapeutic dose be chosen?
- How best to collect and analyze subsequent ECG?

These are addressed in turn.

Maximizing Information from Early-phase Studies

The most appropriate point to conduct the TQT study is arguably as early as it can be meaningfully conducted. Fundamental knowledge of the drug's clinical pharmacokinetics (T_{max} and half-life) is necessary to design the study appropriately, but beneficial preliminary information concerning QT/QTc prolongation liability can also be gleaned from early-phase studies. Certainly, there are challenges in conducting formal, ICH E14-type analyses based on a single early-phase study with a (very) low sample size. Singlet ECGs typically used here (rather than triplet ECGs extracted during the TQT studies) combined with a low number of subjects will almost certainly yield a high one-sided 95% CI upper bound. However, judicious use and combination of data from single and multiple ascending dose studies, along with those from the maximum tolerated dose (MTD) study, can be informative. Data from the MTD

study, along with information from modeling and simulation (discussed in the preceding article) can be of great assistance in choosing the supratherapeutic dose.

ECG Monitoring in Later Studies

The results of the TQT are not to empower a regulatory "approve the drug if all else is OK/fail to approve the drug no matter what" decision. Rather, the true intent, as noted earlier, is to determine the degree of ECG assessment that should be done in later studies to more accurately evaluate the drug's proarrhythmic liability: The greater the degree of regulatory concern generated by the TQT study's results, the more extensive the required monitoring.

In cases where more extensive assessment is conducted, a centralized ECG analysis approach similar to that employed for TQT studies is recommended.[5] While the benefits of centralization have been widely embraced for TQT studies for some time, adoption of this practice for therapeutic confirmatory trials has been less swift. However, awareness is growing that ECG analysis at hundreds of sites by hundreds of individual physicians can be highly problematic. A paradigm shift is occurring in which sponsors are beginning to realize the scientific and clinical (and indeed cost) advantages of ECG centralization in such circumstances, thereby facilitating more accurate and efficient assessment of an investigational drug's cardiac safety.

Development of New Antidiabetic Drugs

New guidances from the FDA[6] and the European Medicines Agency[7] detail additional cardiovascular safety assessments now required during the development of new antidiabetic drugs. Cardiovascular clinical endpoints are to be compared between the investigational drug and control drugs in a meta-analysis incorporating data from the majority of therapeutic exploratory and confirmatory trials conducted throughout the clinical development program. The major adverse cardiovascular events (MACE) composite index, comprising myocardial infarction, stroke, and cardiovascular death, is likely the primary endpoint of choice. Point estimates of relative risk and estimates of their precision (confidence intervals placed around the point estimates) are to be presented to regulators, with the goal of prospectively excluding unacceptable cardiovascular risk. These regulatory guidances have recently been reviewed, and similarities and differences discussed.[8, 9]

Concluding Comment

This paper has illustrated how an integrated cardiac safety program that builds cumulatively during a clinical development program facilitates the accurate and efficient creation an investigational drug's cardiac safety profile, enabling sponsors to present solid data to regulators when requesting marketing approval.

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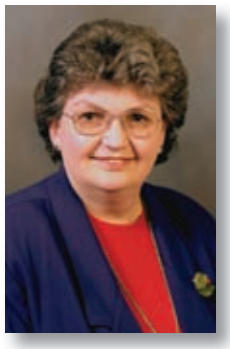
1st DIA Training Forum Held

February 2010

To help professionals in the pharmaceutical, regulatory, and related business areas develop new or more effective training strategies and practices, the **1st DIA Training Forum** convened at DIA worldwide headquarters on February 24. Leaders from the professional training community were invited to share best practices and develop strategies and tactics to help one another's learning, development, and training programs succeed.

Morning sessions featured reprises of three training and learning-oriented sessions from the 45th Annual Meeting in San Diego: *Organizational Learning in the Web 2.0 Environment*, presented by Danny A. Benau, PhD (University of the Sciences, Philadelphia); *Attracting & Keeping the Best Talent in the 21st Century*, by Theresa Hummel-Krallinger (Almac Clinical Technologies); and *Evolution of Learning & Instructional Use of Web 1.0 & Web 2.0 Technologies*, by Pamela Loughner, PhD, Med (Loughner & Associates, Inc.). Roundtable and panel discussions led by Andrea Procaccino, CCRT, CMT (Janssen Pharmaceutical Companies of Johnson & Johnson), who served as Training Forum chairperson, comprised the afternoon sessions.

"Meeting a new group of training/learning professionals with varied backgrounds and expertise from within the industry and having the opportunity to share information with each other and learn from each other was most rewarding," said Andrea. "The rich dialogue that we had around key learning topics that we're all tackling, such as implementing Web 2.0 technologies in learning and learning's role in attracting/retaining talent, was exciting and thought provoking."



Nancy Smith

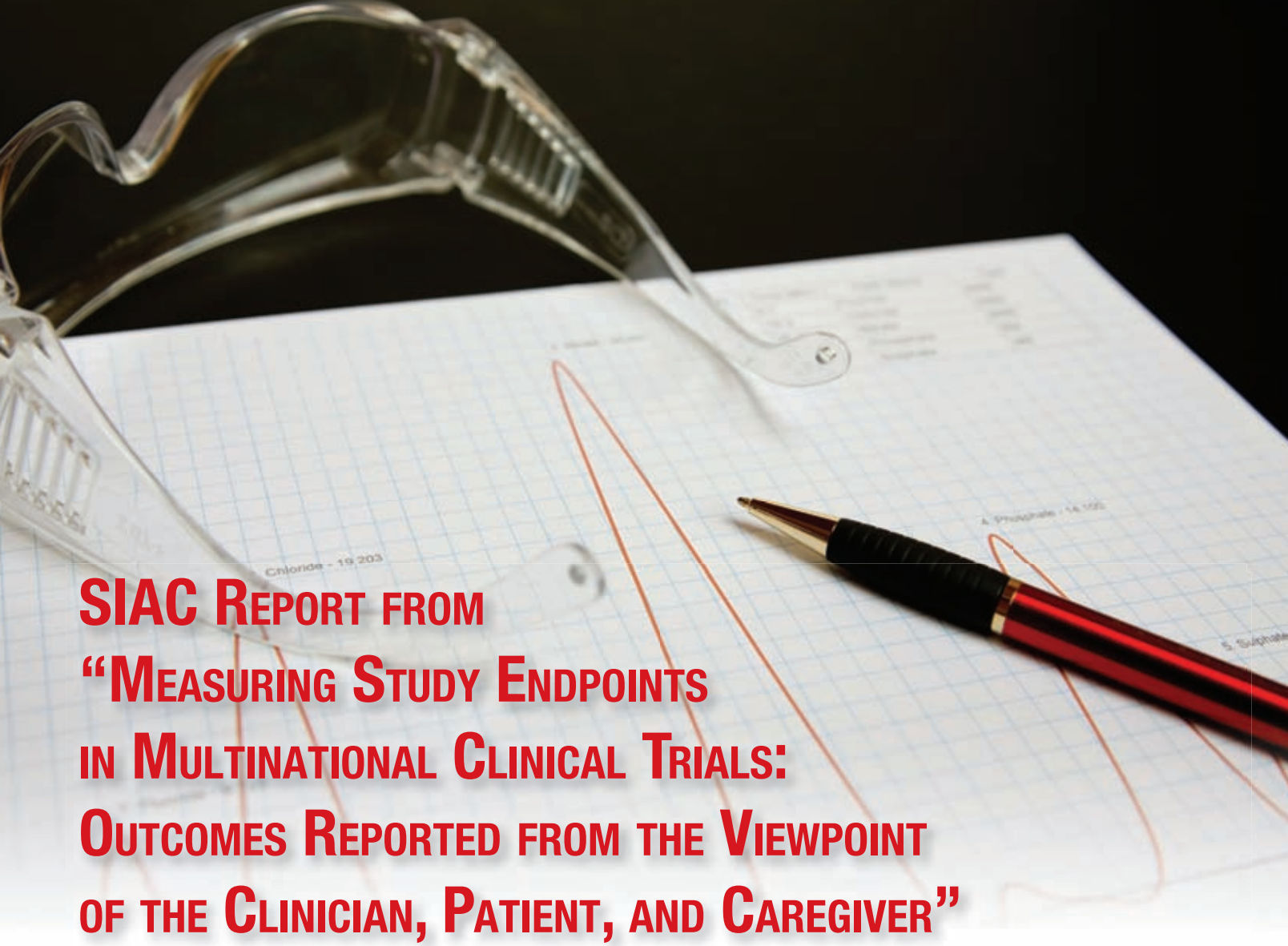
Between the morning and afternoon sessions, a special keynote address was delivered during the luncheon break by Nancy Smith, PhD, Former Director, Office of Training & Communication, CDER, FDA. Nancy, who served as chair for the 45th DIA Annual Meeting in San Diego, encouraged attendees to continue collaborating and communicating with each other to advance their common professional goals.

Throughout this Forum, participants were able to share and discuss common misconceptions about the value of professional development and training, and ways to counteract them. "One of the biggest misconceptions we worked through is that innovative learning and delivery formats are expensive and too complex to use," Andrea explained. "We discussed a number of innovative methods to deliver training and engage employees that utilize available social media and Web 2.0 technologies that are not expensive and are easy to access. These can be employed in ways that can engage employees, cross multigenerational channels, and greatly impact learning retention in the long run."

Andrea Procaccino

Because change in industry and training technologies, budgets, business goals, and regulatory requirements seems constant and certain to continue, DIA plans to convene this unique Training Forum quarterly.

To learn more about the DIA Training Forum, please contact **Jessica Kusma,** DIA In-Company Training Manager, at Jessica.Kusma@diahome.org. ■



SIAC Report from "Measuring Study Endpoints in Multinational Clinical Trials: Outcomes Reported from the Viewpoint of the Clinician, Patient, and Caregiver"

*Contributed by **Jay D. Pearson, PhD** (Merck & Co., Inc.); **Keith Wenzel** (Perceptive Informatics); **Laurie Burke, MPH, CAPT. USPHS** (CDER, FDA); **Jane Scott, PhD** (Mapi Values, UK); **Anna Marie Trentacost** (CDER, FDA); **Elektra Papadopoulos** (FDA); and **John M. Weiler, MD, MBA** (CompleWare Corporation)*

DIA's new Study Endpoints (SE) Special Interest Area Community (SIAC) sponsored a multidisciplinary workshop on October 26-27, 2009 in New Orleans, prior to the International Society on Quality of Life's (ISOQOL) Annual Meeting, to consider study endpoints in multinational clinical trials.

Study endpoints used in clinical trials include, but are not limited to clinician-reported outcomes (ClinROs), patient-reported outcomes (PROs), and caregiver-reported outcomes (CaregiverROs) and other observations of patient signs and behaviors related to health status. These subjective endpoints for medical product development studies are very important to regulatory authorities asked to register new drugs. The use of valid and reliable rating scales as key study endpoints is often central to interpretation of medical product effectiveness and the clinical importance of the treatment effect. The FDA released its final guidance on PRO measurement on December 9, 2009, which provides even more impetus for ongoing discussion on use of these measures in clinical trials.

Recently, there has been significant discussion, but little consensus, on a common set of best practices applicable across all types of report-based measures used as study endpoints. This conference brought together key stakeholders to discuss conceptual, measurement, and practical issues regarding these endpoints when applied to medical product development. The conference included presentations from representatives of the FDA and EMEA who provided multinational regulatory perspectives on the scientific and regulatory challenges of using these types of study endpoints in support of medical product labeling claims.

The conference consisted of four main segments: 1) defining study endpoint terminology within the regulatory context, 2) establishing common principles and best practices for the development and validation of all study endpoint measures, 3) articulating practical considerations when subjective study endpoints are deployed in multinational trials, and 4) setting a research agenda for improving the use of these study endpoints.

The first session, "Defining Terms and Setting the Regulatory Context," proposed a taxonomy of reported study endpoints and discussed how many of the principles of the FDA PRO Guidance can be applied to other study endpoints (eg, ClinROs and CaregiverROs). PROs are reported directly by the patient without interpretation by anyone else; PRO instruments can be self administered or interviewer administered. In contrast, CaregiverROs are reports by a caregiver of observable signs or behaviors by the patient (ie, episodes of vomiting). As direct observations only, CaregiverROs do not include interpretations of the patient's health condition and therefore do not assess symptoms that are only known by the patient (ie, pain).ClinROs are measures of the status of a patient's health condition based on clinical observation and interpretation (ie, vertebral fracture). Some study endpoints are composites and combine several types of outcome measures (eg, PROs, ClinROs, and objective measures (eg, blood pressure or FEV1).

This session also considered the similarities of establishing content validity with PROs and ClinROs and presented the preliminary results of an FDA review of 141 new medical entities (NMEs) approved in the US between 2003 and 2008, which found that 99, 46, and 81 had ClinROs, PROs, and objective measures, respectively. Most NMEs had multiple study endpoint types, but 26% had only ClinROs, 11% had only PROs, and 13% had only objective endpoints. Finally this session reviewed recent European Medicines Agency (EMA, formerly EMEA) approvals to exemplify that the choice of a PRO or ClinRO endpoint depends on the target population, characteristics of the disease, core symptoms and signs, intended claim, evidence of clinical benefit, and endpoint model. Although there is no specific EU guidance, the general principles of instrument validation in the FDA PRO Guidance apply to other study endpoints.

The second session, "Models, Measures, and Claims," considered performance measures such as the Karnofsky Performance Status scale and the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, which are commonly used in oncology trials. Karnofsky and ECOG Performance Status scales are global measures that are very effective in communicating a patient's status in clinical practice but which have significant limitations (ie, high inter-rater variability, low responsiveness) when used as study endpoints in clinical trials. This session also presented limitations of many ClinROs used in clinical research: poor measurement properties, imprecise definition of the concepts being measured, and poor rater training that contribute to failures of clinical trials. Investment in the development of high-quality study endpoint measures is small relative to other costs of clinical development. This session addressed whether patients should be the source of symptom evaluation for adverse event reporting rather than clinicians. Patients tend to report more numerous and severe symptoms than physicians because patients' perspectives are related to their day-to-day suffering whereas the clinician's perspective is oriented towards major clinical benchmarks. However, a standardized adverse symptom PRO may not anticipate novel adverse symptoms that may arise with novel drug mechanisms. The National Cancer Institute's PRO Common Terminology Criteria for Adverse Events project uses a multipronged approach to collecting adverse event data from both patients and clinicians, uses both symptom checklists and ad hoc symptom reporting, captures symptom magnitude, and assesses symptoms between clinic visits.

The third and fourth sessions were titled "Evaluating and Demonstrating Content Validity: Parts 1 and 2" and began with a description of the theoretical and regulatory aspects of content validity. Content validity is the extent to which an instrument evaluates the relevant and important aspects of the concept it intends to measure. Although content validity is most commonly assessed relative to PROs, the same principles are important for all study endpoints. Eight points can be evaluated to determine if there is evidence of content validity: 1) concepts are relevant to patient experiences, 2) saturation of concepts has been achieved so additional testing does not reveal new concepts that require validation, 3) PRO items reflect language used by patients, 4) appropriate aspects of the concept are being evaluated, 5) PRO items can be properly comprehended by patients, 6) response options are meaningful and clear, 7) recall period is appropriate, and 8) concepts and language used in the PRO are adaptable for use in global trials. This session also addressed pitfalls of content validity with various study endpoints that have

been used in gastrointestinal clinical trials. This session described content validity of pediatric instruments. It may be necessary to consider multiple contexts that children experience (eg, school, peer groups, and family). Recall period and comprehension are particularly important issues for pediatric instruments. Content validity is specific to the age group(s) studied.

The session considered CaregiverROs, which are standardized ratings of defined aspects of a patient's health status that require knowledgeable, ongoing assessment by a close observer. The observer could be a health care provider, formal caregiver, informal caregiver, or other informant with sufficient knowledge to provide information. Caregivers may be able to provide information on the disease expression, the patient's experience, or of the caregiver's experience. Finally the session addressed content validity in ClinROs. Standardization of definitions and procedures are critical to ensuring content validity and statistical power of ClinROs when they are used as study endpoints. Loose definitions and broad discretion to use "clinician's judgment" for study endpoints endanger the content validity of the endpoint and increase potential for measurement error.

The fifth session presented multiple practical considerations in the use of subjective study endpoints for multinational clinical trials and real-world examples. The first topic was instrument development for multinational studies including key issues related to linguistic validation and recommendations for overcoming study endpoint development obstacles. With such studies there is a need to a) recognize and understand the challenges faced when assessing study endpoints in international studies, b) plan early and pilot test to address feasibility and critical components to a successful study outcome, and c) ensure adherence to industry standards for translation and cross cultural adaptation. This session described the organization required to use ClinROs and PROs in a 40-country phase 3 study of inflammatory bowel disease. Some lessons learned included the importance of: a) training, retraining, and reminders; b) close monitoring; c) local CRO teams; and d) vigilance to identify trends and red flags. Acting quickly and decisively is vital to success, as is using creative methods for maintaining close control of trials, and ensuring integrity and accuracy of data. The next presentation described the public-private consortium initiative by FDA and several industry sponsors to develop and validate PROs for use in drug development with the goal of developing valid and reliable PROs for specific disorders and contexts of use for qualification review by FDA.

Another presentation provided insights of a physician with respect to use of PRO and ClinROs in clinical drug trials and detailed how it is critical to be sensitive to the burden of the study endpoints in the context of the disease. The final presentation in this session provided examples of technology being leveraged in clinical drug trials including facilitating collection of proxy reports, patient self-report data, clinician adjudication, and maintaining study blind when trial outcomes are unblinded, but vital for patient safety. This session concluded with a statement that: a) technology options are diverse for facilitating endpoint collection; b) technology is being used for more than just collection of efficacy data; and c) technology applications are often limited by creativity versus technical features.

The final session was titled "Defining a Research Agenda for Study Endpoint Measurement and Multinational Clinical Trials," and consisted of three breakout sessions on developing a study endpoint taxonomy, evaluating ClinROs, and evaluating CaregiverROs. Each breakout group identified key research topics that could serve as the basis for working groups within the SE SIAC to advance the state-of-the-art in developing and implementing high-quality PROs, ClinROs, and CaregiverROs.

Look for updates on the SE SIAC in upcoming issues of the *Global Forum*. ■

Review of The Body Hunters:
Testing New Drugs on the World's Poorest Patients

Reviewed by Betty Kuhnert

Sonia Shah: The Body Hunters: Testing New Drugs on the World's Poorest Patients
New York, NY: The New Press, 2006

You should read **The Body Hunters** by Sonia Shah if you have any interest in clinical trials, if you have any interest in the ethics of clinical trials, or if you have any interest in knowing why the pharmaceutical industry has such a bad reputation. The author's bias against pharmaceutical companies, which are portrayed as unethical, is obvious. CROs, who recruit subjects in third world countries, are portrayed as downright evil, and a number of major drug companies and others take some pretty big "hits." Those working within the pharmaceutical or CRO industry will probably not like or agree with many parts of the book, but that doesn't mean you shouldn't read it. It raises many serious ethical and legal concerns about international research that are worthy of further discussion.

The book provides a brief history of the attempts to protect humans from drugs and drug companies starting with snake oil salesmen and the first requirements for tests of efficacy and safety. Unfortunately, according to the author, requirements to demonstrate efficacy and safety led to the requirements for clinical trials and to all the inherent abuses therein. Two of the major abuses are the need for placebo-controlled clinical trials and surrogate endpoints, which the author feels are inherently unethical.

The book also gives a brief review of ethical guidelines for clinical trials starting with Nuremberg and going to recent revisions of the World Medical Association's (WMA) Declaration of Helsinki. However, the author makes the assumption throughout the book that these guidelines are rarely followed by those doing clinical trials, and ethical oversight is particularly lacking when the research is done in developing countries. Furthermore, in the chapter called "Calibrating Ethical Codes," the author suggests that there is collusion between the FDA (and presumably other regulatory agencies) and the pharmaceutical industry to put pressure on the WMA to weaken patient protection.

The history of unethical clinical trials is summarized starting with the Tuskegee study, moving through several placebo-controlled vaccine or HIV transmission studies in Asia, the Pfizer Trovan® antibiotic study in Nigeria, and ending with the Jesse Gelsinger tragedy in Philadelphia. Thus, this book is an excellent reference for those interested in the ethics of clinical trials. However, the author seems to miss the point that many of these studies were not done by pharmaceutical companies, but by government agencies, academics, or sponsor-investigators. The author also leaves the reader with the impression that nothing is being done to counter unethical practices. She does concede that had some of these investigations been done for submission to the FDA, they would have been closely monitored.

Informed consent is discussed in a chapter entitled "The Emperor Has no Clothes": The author's premise is that it is probably impossible to get informed consent, particularly in developing countries where patients may be illiterate and there may not even be words in local languages for concepts such as "experiment" or "placebo." CROs prefer uninformed, coerced subjects, according to the author, and not only is informed consent an impossible standard, uninformed consent is practically a necessity for doing clinical trials.

Testing New Drugs on the World's Poorest Patients, the book's subtitle, refers to valid issues that the author raises about doing clinical trials, ethical or unethical, in developing countries. Uninformed consent is only one issue of concern, along with exploiting poverty, undermining human rights, or misallocating resources. Specific issues

include the social distance between investigators and poor patients, substandard treatment, lack of follow up, the use of local IRBs, and incentives such as money, medical care, and food. A whole chapter is devoted to India, where local IRBs supposedly earn money rubber stamping studies without caring about the subjects they are supposed to protect.

The author concludes with a plea for public and nonprofit drug companies who will regain public trust by making medicines not as a business but as a public health effort. Although the reader may not agree with everything in this book, it ends with the following statement that is hard to argue with: "But medicines are not just commodities, they are social goods, and their development requires experimentation on humans. So long as that remains true, we need to find ways to do it right, and to do it fairly."

Despite the obvious bias against pharmaceutical companies and CROs, and the author's misleading impression that nothing is being done to counter unethical practices, the book is a good read. ■

Betty R. Kuhnert, PhD, MBA, *is Executive Director, Training Services, at PharmaNet and a member of the Editorial Board of the* Global Forum.

TWELVE WINNING WAYS

TO BREAK THROUGH JOB INTERVIEW BARRIERS

So you're in the job market and you think you are ready to meet potential employers in person. Your resume, which reflects your in-depth industry knowledge, as well as your core capabilities, has been thoroughly proofread by several unbiased sources. You know of several firms where you would like to work. You are also about to prepare individualized cover letters to several job leads provided by past employers and networking colleagues.

It seems as if you have your bases covered. But wait. Before you proceed further in your job search, let's explore the "ins and outs" of job interviews. What different types are there? How can you prepare? What questions will you need to answer? What should you ask of prospective employers and when?

INTERVIEWING 101: UNDERSTAND THE PROCESS

Having answers to the above questions—and many others—is vital. That's because the job interview is a crucial step on the ladder towards reaching new employment.

"The point of each interview is to get to the next interview, with the ultimate aim of obtaining the job offer," says Tony Beshara, executive recruiter with Babich Associates in Dallas, Texas and author of the book Acing the Interview. In fact, you should "plan each interview as if it were a job project with a goal in mind—which is to get the job," adds human resource consultant Rita Auld.

So roll up your sleeves. Arming yourself for today's job interviews requires research, time, perseverance, and hands-on practice. Here is a step-by-step approach.

1. CARRY YOURSELF WITH CONFIDENCE

Feeling good about yourself and your job history will lead to an air of self-assurance and confidence in your professional skills that others can detect. Unfortunately, "many of my clients have failed to impress interviewers because they unknowingly carried emotional baggage that negatively affected their mind-set and subsequently their demeanor," reports Beshara. To prevent this, he recommends that you assess why you are not currently working. Ask yourself, "Were the problems on the job my fault or the fault of others?" (For example, if you were laid off, it was clearly not due to poor job performance.) Keeping this in mind can improve how you "carry yourself" and how interviewers may perceive you.

2. HAVE YOUR RESPONSE READY

Be prepared to answer these questions: "Why should we hire you?" and "Can you do the job?" To reply most effectively, Beshara suggests you create a "benefit statement that encapsulates why you are the best candidate." Include in it a summary of your skills, what you did for your former employer and how, and what, you can do for the prospective employer. For example, a pharmaceutical sales executive's benefit statement could be: "I am thorough and detail oriented. I keep up with research on existing products and I carefully study new offerings. I implemented a system to keep in touch with nurse practitioners and physicians' assistants; I love what I do."

3. STUDY POTENTIAL COMPANIES

Ronald Kaufman, executive coach and president of Ronald A. Kaufman and Associates in Los Angeles, California, categorically states that "your interview begins with your initial research into each prospective employer." Auld, who is a former vice president of a small global specialty pharmaceutical company and is now principal of Auld Consulting LLC, in central New Jersey, wholeheartedly concurs: "Interviewees need to have a knowledge base," she says "to answer a number of questions,

including "How is the company faring? How is its stock doing (if a public company)? What is the firm's latest news event?"

All human resource experts emphasize that it is imperative to consult the Internet and social media tools to find information about prospective employers and the people who work there. (The same findings should also be utilized to prepare customized introductory cover letters for each position.)

4. KNOW YOUR INDUSTRY

All interviewers must display knowledge of their business field, their skills, and their job functions, according to Auld, an HR consultant for a number of biotech and pharmaceutical companies. For example, she says typical job interview questions for a research scientist might include: "Who were the key opinion leaders and what products were you associated with in your past positions? Do you know the key 'movers and shakers' in this (the prospective employer's) company?" A typical line of questioning for an entry level pharma rep might be: "What are the products you most recently sold? Is it an injectable, a topical, or a radiopharmaceutical product? Where and to whom did you sell?

Have you sold to primary care physicians or to specialists in the field that our product is sold to?"

TYPES OF INTERVIEWS

Different styles of interviews are utilized by potential employers to uncover how well you solve problems and relate to various personality types and situations.

Phone Interview: Screens you to see if you can be eliminated from the list of candidates. **How to Respond:** Executive recruiter and author Tony Beshara offers all the advice on this screening process: If you can't talk in private, arrange to call him back. The interviewer, who may be a recruiter or an entry-level, in-house human resource employee, is trying to eliminate you. Don't let them!" Listen carefully to the questions before you answer (this applies to all interviews). Find out all you can about the job, including the responsibilities, the next step, names of key personnel. Do not broach the subject of salary. If asked, say you are "open," relates author Marky Stein.

Behavioral Interview: Explores how you achieved your job goals in your past positions. **How to Prepare**: Prior to interview, scan your resume to create two-minute-long, logical stories that explain what you did, how you did it, with whom, and the results.

Interesting Fact: Most widely used interview method.

Directive Interview: Interviewer maintains tight control over the discussion* by utilizing pointed questions. Kashlak-Nicolai explains this interviewer is a "non-relationship-building leader" who dislikes "chit-chat." **How to Respond:** Kashlak-Nicolai says, "Stick to short, succinct, bullet-point answers." **Important to note**: Would you prefer not to directly report to this style of leader?

Pattern or Structured Interview: Interviewer presents a problem the company has already solved.* Asks, "How would you solve this problem?" **How to Prepare**: Discover industry trends by reading trade journals; read company's press releases to become aware of the specific situation. During the interview, also indicate networking peers who might trouble-shoot and assist you with possible solutions.

Non-Directed Interview: General questions give you an opportunity to highlight your own positive experiences. **How to Respond**: Use stories to illustrate how you have solved problems in your previous positions. Know industry and company problems and relate your experience to how you would solve a specific situation.

Stress Interview: "Intimidation tactics…. long waits before interview… uncomfortable silences… brusque interviewer." **How to Respond:** "Speak with calm, unflagging confidence."* Important to note: Do you thrive or prefer not to work in this type of stressful environment?

Information noted with an asterisk (*) is from Job Interviews for Dummies by Joyce Lain Kennedy; Wiley Press, 2008. Unless noted, all other materials were supplied by professional career strategist Tina Kashlak-Nicolai, Orlando, Florida.

Auld further points out that those seeking a position that has more than one point of sale will face a more complex level of questioning. For example, seasoned pharmaceutical executives might need to answer: "Do you have the advanced training and scientific background that allows you to deal with physicians, such as urologists and oncologists, who will be using the products you will be responsible for selling? How do you sell a product that requires coordination with several departments?"

JOB-LANDING TIP: If you are a viable candidate you will have more than one in-person interview. After each interview, remember to send an email, or a typed or handwritten thank-you to each interviewer.

5. BE ARTICULATE

Hiring professionals agree that candidates need to express themselves concisely and lucidly to convey their aptitude and experience. Tim Ragan, principal of Career Coaching International of Ottawa, Canada, advises that you "speak directly to answer the interviewer's questions clearly and succinctly. Don't ramble and 'talk yourself out of the job.'"

Boston job coach Wendy Gelberg added that rambling "may be a problem for extroverts, who tend to talk while they think. On the other hand," she says, "since introverts tend to think before they talk, they must focus on the questions and fight the instinct to want to go away and come back later with the answers." Speaking plainly and effectively may also be difficult for "those who do not like to brag." Instead, she advises to "try thinking of the interview as a conversation in which you are just reporting the facts."

Importantly, keep in mind that communicating well can help you break ahead of the pack. Auld says that outstanding candidates have the ability to "answer unexpected questions" and to "portray their capabilities in a professional manner…and with an air of confidence—and that happens because of preparation."

6. WATCH YOUR BODY LANGUAGE

How your body reacts during the interview can speak volumes. Keep a positive state of mind and avoid sending "mixed messages." For example, Kaufman has seen individuals talk positively about a situation while shaking their heads side to side (which indicates a "no"!).

Also, don't cross your arms in front of you; it makes you seem unapproachable and secretive, says John Haynes III, human resource manager at Johnson Controls in Maryland, a worldwide company that builds efficiency and power solutions for automobiles. Marky Stein, the interview expert on monster.com and author of Fearless Interviewing—How to Win the Job by Communicating with Confidence adds, "Don't slump back in your chair, which makes you look lazy; sit forward so you look enthusiastic and engaged."

Other interview and etiquette tips:

- Engage the interviewer in the first seconds of meeting
- Look the individual in the eyes
- Firmly shake his or her hand and introduce yourself with your first and last name
- Ask permission to sit down and do not sit before the interviewer
- Stand up when someone else enters the room

7. KNOW HOW TO RESPOND

Familiarize yourself with a variety of interview methods and the questions involved in each. Sidebar 1 talks about what you can expect and suggests ways to effectively deal with each situation.

8. EXPECT MULTIPLE INTERVIEWS

Most companies use recruiters or lower-level, in-house human resource personnel to screen prospects with an initial telephone interview. (See Sidebar 1.) Subsequently, how many people interview you and their positions in the company depend on each firm and the job you seek.

That is true at Johnson Controls. According to Haynes, the process may initially involve an outside recruiter or hiring manager and/or an interviewing team. If interviewees pass these hurdles they might then meet with a mid-level manager or an upper management/executive level individual, depending on the level of position sought.

9. PRACTICE, PRACTICE, PRACTICE

You have to be prepared for each interview, says Beshara. "The worst thing you can do is say to yourself *I am good at winging it*. That kind of overconfidence and lack of preparation can do the worst disservice to even the most qualified candidate."

One way to prepare is to create hypothetical interview questions—and answers—based on the job description, suggests John Rorick, Director of Recruiting, Canon USA in Lake Success, New York. "By practicing over and over, on your own, you will relax and be more confident during the interview."

In addition, he and numerous job strategists strongly suggest that you stage and then videotape a mock interview with a family member or friend. (Better yet, if you can afford to, hire a career coach.) Get feedback

on eye contact, tone of voice, level of enthusiasm and speed of speech. (Try to speak at about the same speed as the interviewer.)

Gelberg agrees on the value of taping mock interviews, as does Kaufman who adds, "You may not be aware of how you fidget or what tension you are holding in your face while interviewing… My clients really 'get it' when they see and hear how they behave on tape."

JOB-LANDING TIP: Don't ask "What is in it for me?" questions. Ask yourself, "How can I fill the needs of the prospective employer?"

10. LEAVE ON A POSITIVE NOTE

During the interview keep a small pad on your lap and check to make sure you have emphasized all your important points, recommends Gelberg. Also, in closing, Beshara says, you should reiterate the following: "As you know, I am very interested in working for your company. Here is what I bring to the table: (add three or four specific skills, traits, or behaviors.) Importantly, ask the interviewer how you stack up against the other applicants. Ragan strongly advises interviewees to ask about the next step in the company's hiring process; initiate a plan to follow-up and follow through accordingly.

11. KNOW WHEN TO NEGOTIATE

Stein advocates the use of the "open door policy" when negotiating salary. In the first interview, or in a phone screening, it is better to say that your salary is "open, flexible or negotiable. Let the interviewer be the first to bring up a number. If you must speak in numbers, speak in a range of salary rather than getting stuck on just one number."

Formal discussions about compensation usually take place at the time of the job offer. Be prepared. Kaufman advises know your minimum yearly, monthly or weekly salary and when the offer is made have a neutral reaction. (If you express excitement the interviewer may think he offered you too much.) If the number is too low, respond by saying, "I am very interested in working for you. Based on my training, skills, experience and education I was anticipating a higher number."

Make sure you know ahead of time what aspects of your profession you like—or dislike—and what benefits you want, advises Ragan. This is essential in evaluating a job offer and in negotiating your salary and job perks. "If you don't know what you want how will you be able to negotiate for it?"

Ragan also reminds candidates to have a clear vision of what is important to them. For example, do you want to spend time with your children or advance your career training? Also keep in mind that, in addition to your base salary, tuition reimbursement, flex-time and telecommuting can add considerable value to the overall package.

12. STAY IN TOUCH

While the interviewing process is stressful, remember that job interviews are meant to benefit both you (the applicant) and the prospective employer. While the company needs to confirm whether your skills, experience, and temperament match its goals and corporate culture, the interview is also your opportunity to evaluate whether you think the position is a good fit for you.

Differentiate yourself from other applicants by researching (Internet, industry publications) and proposing a solution to a problem the prospective employer is experiencing. John Haynes III of Johnson Controls has hired at least one individual who brought such a proposal to an initial interview.

If you do not receive a job offer, communicate to the interviewer that that you would like to maintain contact—and then follow up responsibly, with restraint and in a businesslike manner. Rorick says Canon welcomes qualified candidates to keep in touch. He adds, "We especially like to keep people in mind who can relate their experience in an articulate manner."

In the meantime, keep a positive attitude, continue to conduct research, make contacts, and practice interviewing. As Beshara notes, "It is not the best candidate that necessarily gets the job. It is the candidate who does the best job in the interviewing process!"

Best of luck! ■

For *Extraordinary Measures* Dad, Medical Research is All About Hope

John Crowley remembers hearing the late actor Christopher Reeve once say, "At the end of the day, biotechnology is really just a great big word for hope."

John, whose story is chronicled in the new movie *Extraordinary Measures*, understands better than most just how powerful hope can be.

John's extraordinary journey began in March 1998, when his 15-month-old daughter, Megan, was diagnosed with a rare and nearly always fatal neuromuscular disorder called "Pompe disease." Doctors told John and his wife, Aileen, there was a 25% chance that their week-old son, Patrick, also had the disease. A few months later, Patrick was definitively diagnosed with Pompe. At the time, children with Megan and Patrick's atypical strain of Pompe weren't expected to live past five years old.

"You think, 'this is not supposed to happen to us,'" says John, who had never heard of Pompe disease. "You go through the shock and denial and grief."

Pompe disease is a disorder caused by a deficiency in the enzyme that breaks down sugar (glycogen) and converts it into energy. The build-up of glycogen causes muscle weakness, particularly in the heart, skeletal muscles, liver, and nervous system. If untreated, patients eventually lose the ability to eat, breathe, speak, and walk. Ultimately, many suffer from heart and respiratory failure.

Pompe affects fewer than 10,000 people worldwide. The disease is so rare, the neurologist who diagnosed Megan had never seen a case before, and no company had yet developed a medicine to combat it.

John's reaction to the diagnosis was typical of what any parent would experience when blindsided by such devastating news. So was his next step: he learned everything he could about Pompe disease and the research relating to it. Then he did something extraordinary: he stepped in.

In 2000 John teamed up with Dr. William Canfield, an Oklahoma-based biochemist who was developing an enzyme therapy for Pompe disease but lacked funding for clinical trials. John, a Harvard-trained MBA, left his job as an executive with Bristol-Myers Squibb Co. to become CEO of Dr. Canfield's fledgling company. He took out a second mortgage on his house to help finance the company, raised tens of millions of dollars from venture capitalists to shepherd its drug development program, and ultimately sold the company to a larger firm, Genzyme, to help secure its future. John's story as a father turned advocate turned biotech CEO may be unique, but sadly his experience as a father desperate to obtain life-saving therapy for his sick children is not. In that regard, John is the quintessential spokesman for families seeking therapy. He understands all too well what clinical trials mean to families combating fatal diseases.

For patients and their families, "the trial is the realization of hope," he says. "I think everybody goes into a study with the feeling that it gives them that much more hope: hope that maybe life will be a little bit longer or a little bit better, all the way to the point of hoping, 'Gosh, maybe we'll beat this thing.'"

But that hope comes at a price. Qualifying for a trial and the pace at which the trial process moves can be infuriating for patients and their loved ones. John's children were too old to participate in the first two phases of clinical trials for the new Pompe therapy and were initially disqualified from a third phase because the institutional review board (IRB) at Children's Hospital of Philadelphia felt John's position as a Genzyme executive posed a conflict of interest.

During that time John watched his children grow weaker every day. "The time it takes for individuals to become qualified for studies and for studies to advance through the system is brutally difficult" for patients and their families, he says. It's nearly impossible for an anxious patient to distinguish between the

necessity for rigorous scientific protocols and bureaucratic red tape "because you're on the outside."

He faults a cumbersome IRB review process, which can take many months, with exacerbating the problem. Because many IRBs meet monthly, questions raised at one meeting may not be addressed until the next meeting. Answers to those questions may spark follow-up questions and the process is repeated. "It can take eight or 12 or 16 weeks to answer a handful of questions," John complains. "As a patient you don't understand. You're thinking, 'Wait, I thought the study was beginning in April and now you're telling me it may be another year before I can get the drug?'"

John cites his own experience with the IRB at Children's Hospital of Philadelphia as an example. "It took four months for Children's to come up with 'no' for an answer."

And, of course, there are the risks. Megan and Patrick were finally accepted into the third phase of the Pompe enzyme trial at St. Peter's University Hospital in New Brunswick, NJ, in January 2003 after John had resigned from Genzyme. Before they could receive therapy, however, the Crowley children had to have an infusion port inserted in their chests. Patrick barely survived the nearly four-hour procedure.

John vividly remembers the surgeon emerging from the operating room after inserting Patrick's port and throwing his mask on the floor. "I hope that was worth it," he said.

Surviving the surgery was just the first hurdle, John notes. Between 5 and 10% of the children receiving the Pompe enzyme therapy have an anaphylactic reaction. Others develop antibodies to the treatment and of course, there's always the looming question: Will we be able to continue to get the medicine?

Hollywood loves a happy ending, and the fact that Megan, now 13, and Patrick, 12, are alive today is testament to the power of clinical research and their father's unwavering dedication. Their hearts and livers, once dangerously swollen, have returned to normal size, and the disease is progressing in their skeletal muscles much more slowly than it would without the treatment. The children continue to receive the enzyme therapy every other week, but their health is fragile: both still depend on wheelchairs and ventilators and need full-time nurses.

John celebrates his children's achievements and relishes their plans. He notes that Megan, a seventh grader, hopes to attend college at Stanford and has already picked out the church where she'd someday like to be married. While Megan dreams of somedays, John continues to search for a new and better treatment for Pompe because the current enzyme therapy "is not the final answer."

For patients, medical research is a long and arduous road. But it is the only road, John says.

"This is how we translate ideas and results that look good in animal studies into treatments. This is how we learn. Where would we be today if we didn't have people who were brave enough or willing enough to participate in phase 1 leukemia trials 30 years ago?" he asks. "The treatments that came out of those trials have resulted in survival rates going from 5% to 90%."

Research is hope, and hope does not stand still. "The hope overwhelms the fear," he says, "Especially when you see early signs of success." ■

John Crowley

This story is from a series of articles created by CISCRP as part of their educational awareness campaign to increase public understanding that those who volunteer to participate in clinical trials are genuine "Medical Heroes."

MARKETPLACE

DIA Members on the Move

DIA is committed to improving the professional performance of our members and volunteers through our educational and networking forums. Please join us in congratulating the following DIA members for their recent professional accomplishments:

Kay Bross, MEd, was appointed Program Director, Member and Vendor Relations, for the SAFE-BioPharma Association.

Mark W. Davis was appointed Vice President, Clinical Development, of Topica Pharmaceuticals.

Glen de Vries (Medidata Solutions) has been named one of *Crain's* "40 Under 40," an annual list of rising business stars who have excelled in their respective fields.

Frank Gallo was appointed Executive Director of Risk Management for PPD, Inc.

Kristina A. Gartside (Shire Development Inc.) was recognized by Cambridge Who's Who for showing dedication, leadership, and excellence in pharmaceutical technical editing.

Becky Mae Ingram (Medicis Global Services Corporation) was recognized by Cambridge Who's Who for demonstrating dedication, leadership, and excellence in knowledge and federal regulations.

Lisa Jenkins, PhD, was appointed Director of Regulatory Strategy of Image Solutions, Inc.

Guido Roumans was appointed Director, Global Life Science Services, of TechTeam Global, Inc.

Robert Sammis, MBA, was appointed Vice President of Finance, eClinical Division, of BioClinica, Inc.

Dale Trask was appointed Vice President, Global Business Development, of Venn Life Sciences. ■

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