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Harmonization– A Vision in the Making

ANDRZEJ CZARNECKI
EDITOR-IN-CHIEF

Many different factors can lead to progress. Which of the many factors has the greatest importance is a highly debated issue. Looking back, one could mention, for example, simple chance, startling idea, or short- or long-term vision. All three of these examples can lead to substantial change in various ways, which can be different relative to science, life, processes, and also can affect the development of a way of perceiving the world or just a simplification of what we do.

The main topic of this month's *Global Forum* is the International Conference of Harmonisation (ICH). We have referred to ICH many times in previous years. However with the 20th anniversary of ICH 1, which took place in Brussels in 1991, we felt that it would be a good opportunity to look back at the early days of the process and some of the outcomes that we benefit from, seen from the perspective of people who were involved from the birth of the idea in 1989, in the first conference two years later, and throughout the subsequent years. It is worthwhile to go back in time and see this process through the eyes of contemporary witnesses and contributors, some of whom have provided the articles for our special section in this issue.

Over 20 years ago, a group of people had a vision of how health care systems and patients in particular could have much quicker access to new, innovative, and more effective treatments. They foresaw that if

the appropriate agreements could be reached in the three major pharmaceutical markets of that time, then the goal would be achieved. The leading idea was simple—to agree on and harmonize the regulatory requirements with respect to the submission package to receive a license. Such a solution would decrease the workload needed to satisfy different regulatory authorities and allow for one dossier to be used across different geographies. This vision was somewhat futuristic, and was based on the presumption that it is possible and doable to reach an agreement between the regulators, scientists, and pharmaceutical industry with respect to the content and format of the submission package. The original concept planned that three conferences, each held in a different region, would be sufficient to discuss and agree on the topics of interest. Soon into the process however, it became clear that the full benefits would only be achieved if many more topics were opened for discussion. This broader approach required much more time and the involvement of many more experts. As this started happening and the harmonization of data for a standard submission package was progressing, other topics were delivered as well. For example, in the efficacy topic (E), postmarketing safety data were addressed creating ICH E2C (PSUR) and ICH E2A (expedited reporting), both of which were finalized during ICH 3 in Yokohama, which was meant to be the last of the three planned conferences.

With the passage of time, developing knowledge and the realization of current and future needs expanded the ICH process even more and, as we are all aware, it continues to deal with new topics and the necessity of revising previously addressed ones. It is important to keep in mind that the original idea created a significant foundation for the development of cooperation between scientists across the world to deliver the highest standards and agree on them, with the goal of maximizing benefits.

Many individual experts who were involved in the ICH process parted from this activity over time, which is not surprising for a 22-year period. They were replaced by new ones from industry and the regulatory and scientific communities, and joined working groups to deliver new documents that allow us to work better and more efficiently. It is important that those who are part of the process today, but also those outside of it, remember that the vision that brought us together helped many patients across the world get better medicines sooner. It also helped regulators and industry to develop better evaluation methods and to increase their understanding of progress in the pharmaceutical area. It saved a lot of assessment time, which directly translated into benefit for "customers."

When new ideas or hurdles emerge it frequently may seem that it would be easier to "go separate ways," and skip or avoid discussions with other parties, but such considerations should be seen not only as a setback to the original, successful vision of harmonization, but also potentially to society and patients.

After 20 years, a substantial number of activities in the pharmaceutical field can be perceived from the harmonized or disharmonized perspective. There are many parts of the world that were not a party to the original ICH process, and are not a part of it today, but they can benefit from implementation of ICH documents and align with the other countries/regions to benefit from the expert work delivered over time.

The *Global Forum* has always been supportive of a common understanding and fulfilment of agreed-upon standards across the world. In the "Best Practices" section, we publish many articles from different countries and regions, whose value would be entirely different if the "practices" did not follow ICH guidelines. I always encourage readers to look through this section, which in this issue provides an article on clinical trials in Korea, presents interesting aspects of outsourcing, and offers approaches to operations and budgeting in clinical trials.

I would like to take this opportunity to thank Betty Kuhnert, a member of our editorial board, for taking the role of the editor of the special section in this issue. In her introduction to the section, Betty provides a quick history of ICH, as well as an overview of the topics discussed in the articles. Let us all hope that the, by-now matured vision born in the late 1980s, will continue to serve everyone well in developing new requirements and standards, and implementing the existing ones across the world and for all patients. ■

Harmonization

DIA Vision

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

RICHARD DAY

Harmonization – bringing together in harmony, in accord, or in agreement – is happening all around us.

Harmonization helps us work together better. Much of this global harmonization wave in industry, science, and regulatory strategies and approaches, is cresting, thanks to DIA members and volunteers and our efforts focused on advancing operational, scientific, and regulatory harmonization around the world.

Working together better is so deeply ingrained in our educational workshops, conferences, and training courses, that you'll find it almost everywhere you look:

- In Panama City, Panama: DIA's Latin American Regulatory Conference (LARC) 2011: Harmonization of Regulatory Requirements in Drug Development & Registration will include an update from the Pan American Network for Drug Regulatory Harmonization (PANDRH) and on the state of harmonization in the Asia-Pacific Economic Cooperation (APEC) member nations

- In Seoul, Republic of Korea: In partnership with the International Federation of Pharmaceutical Manufacturers & Associations and the APEC Harmonization Center (AHC), we will collaboratively present DIA's first Asia Regulatory Conference: Asia's Role in Global Drug Development; convened to recognize the launch of the AHC, this will bring together representatives from numerous Asian and ICH regulatory agencies to discuss and update harmonization efforts by member nations of the ICH, APEC, and Association of Southeast Asian Nations (ASEAN)

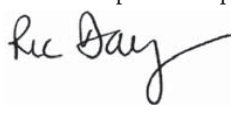
- At EMA headquarters in London, and everywhere else in Europe where DIA serves as organizer for standardized EudraVigilance training, collaborating to help harmonize the conduct of pharmacovigilance throughout the European Union

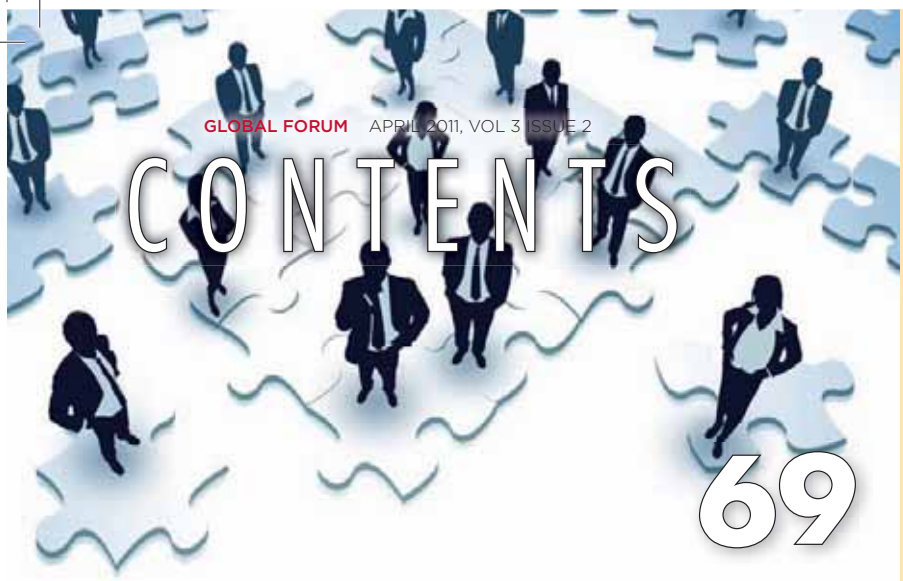
- In North America: Upon the conclusion of our recent biennial CMC (Chemistry, Manufacturing, and Controls) Workshop: Translating Science Into Successful Regulatory Submissions in Washington, DC, leadership from the FDA and EMA jointly announced the latest in the agencies' series of collaborative pilot programs: A pilot for joint EMA/FDA review of the quality-by-design component of new drug marketing applications, another step down the harmonization pathway

- In Europe and in North America, where DIA has worked and continues to work with the EMA and the FDA for two training courses and a workshop to help prepare for implementation of the new ICH Guideline for Individual Case Safety Reports scheduled for later this year

- Did you think we forgot cyberspace? Attendees at our recent 23rd Annual EuroMeeting were provided a digital, mobile application to download program information and receive timely information updates; a mobile app is being developed for our upcoming DIA 2011 Annual Meeting, too. DIA members with iPads and iPhones will soon be able to digitally download current issues of their *Global Forum* and *Drug Information Journal* member publications through a free Apple mobile app.

This issue of your *Global Forum* includes articles on many of these activities, plus a special section dedicated to harmonization and related subjects. Please join me in extending thanks to Betty R. Kuhnert, PhD, MBA (PharmaNet) for serving as editor of this special section, and to every author who contributed an article on this special and quite timely topic. ■





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The *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 updates and news of the association and its programs. The magazine is circulated six times a year as a benefit of DIA membership.

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Harmonization, Not Replication

PAUL POMERANTZ

It is interesting to reflect on the extent to which the history of DIA parallels the modern era of pharmaceutical regulation and how our global activities parallel the emergence of international harmonization.

The 1960s represented a revolution in FDA regulatory authority. The most important change was the requirement that all new drug applications demonstrate "substantial evidence" of the drug's efficacy for a marketed indication, in addition to the existing requirement for premarketing demonstration of safety. Shortly thereafter, the European Community introduced the mutual recognition and centralized procedures. These activities set the stage for future global regulatory harmonization.

The need for wider harmonization led to the establishment in 1990 of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan, and the US with observers from WHO, EFTA, and Canada. The creation of the ICH has resulted in great progress in the harmonization of the regulation of medical products.

Mandated by the increasingly global nature of medical product development, harmonization can only help our industry improve efficiency and ensure that everyone, regardless of geography or socioeconomic status, has access to the medical products they need. However, harmonization is a means, not an end. It is a process that is never complete. With new science and global concerns over safety and quality, harmonization faces new challenges, and DIA forums provide critical opportunities for stakeholders to discuss solutions. The "new frontiers" for harmonization include information and data standards as well as the regulation of medical devices, combination products and advanced medical technology, and the evolution of health technology assessment.

Harmonization is the focus of this issue of the *Global Forum*, and I would like to thank Betty Kuhnert, Executive Director of Training Services at PharmaNet Development Group Incorporated, who so capably served as section editor for this group of articles.

Today, the boundaries between classes of medical products are rapidly blurring. Increasingly, medical devices integrate diagnostics with drug delivery or serve as sophisticated delivery systems. Nanotechnology and other advances pose new challenges to our regulatory system. Although, the Global Harmonization Task Force (GHTF) was conceived in 1992 in an effort to respond to the growing need for international harmonization in the regulation of medical devices, our regulatory system has lagged relative to medical devices. In response, the FDA recently announced plans to spend $25 million in 2011 on research in some key areas, including the use of biomarkers for personalized medicine, better data collection on outcomes for medical devices, and how to scientifically assess new technologies in FDA-regulated products.

DIA is exploring unique opportunities through the work of our Medical Devices Task Force (MDTF). The MDTF, chaired by Board member, Dr. Steve Caffe, worked throughout 2010 to address issues such as the state of medical device product development and regulation, with a particular focus on combination products, and potential offerings by DIA. A new MDTF will begin work in July. Its mission will be to provide strategic advice on programs focusing on combination products,

nanotechnology, intelligent devices, and other advanced therapies. The work of the MDTF will be expressed in the June *Global Forum* (special focus on medical devices) and in a range of programming at the Annual Meeting. While the initial Task Force was focused on North America, the new iteration will take a global view.

But we will not end there. Rising costs for health care represent a central challenge for both public and private payers in virtually all countries. Generating better information about the costs and benefits of different treatment options—through research on the comparative effectiveness of those options—is credited by policy makers with the potential to optimize quality while limiting costs. To this end, DIA will leverage the learnings from our Real World Outcomes Task Force (RWOTF), co-chaired by Dr. Richard Gliklich, and Board member Dr. Judy Glennie. This group is exploring opportunities for a more harmonized environment for comparative effectiveness research, and is addressing topics including training of researchers, terminology, and creating an inventory of work of related organizations worldwide. In addition, a special forum at the EuroMeeting is convening thought leaders from both Europe and North America to discuss where DIA can support the needs of health technology assessment processes, and in particular, their interface with the regulatory system. We will keep you informed on these discussions.

DIA is evolving to serve a dramatically new health care landscape. Regulatory harmonization has been successful because it has continuously evolved to meet emerging needs. Global standards have been developed in neutral forums, with the engagement of all stakeholders. DIA has been an important part of the process by providing a forum where needs are identified and standards debated and disseminated. On this, the 20th anniversary of global regulatory harmonization, DIA is honored to be part of its history, and looks, with responsibility, toward its future. ■

CLINICAL TRIALS IN SOUTH KOREA:

Becoming a Leader in Asia's Life Science Arena

Min Jung Park, Young-Ok Kim, and Yun-Hong Noh

Background

The Asian clinical trial market is growing rapidly and the infrastructures of the involved countries are being systematically revised and reorganized in terms of their own regulations and management. Although North America and Eastern Europe are still the world's leading regions for clinical trials, it is clear that the competitiveness of clinical trials and the development of new drugs are moving toward Asia Pacific and the BRIC (Brazil, Russia, India, China) countries.

In 2009, a total of 400 clinical trials (202 multinational and 198 local) was registered with the Korea Food and Drug Administration (KFDA) (Figure 1). Data showed that phase 3 trials predominated, accounting for 59.9% (121/202) of all multinational trials, while phase 1 trials predominated with 39.4% (78/198) among all local clinical trials (Figures 2 and 3). Oncology studies predominated in both multinational and local trials in 2009, comprising 33% and 19%, respectively (Figures 4 and 5), followed by cardiovascular and central nervous system studies. In 2009, Seoul was still the most active city for clinical trials, conducting 70.5% and 66.4% of multinational and local clinical trials, respectively. Dae-gu and Busan contributed 5.2% and 5%, respectively, of multinational investigations, and Dae-Geon and Busan contributed 6.19% and 6.04% of local investigations (Figures 6 and 7).

South Korea launched the Korea Food and Drug Safety Headquarters (KFDSH) in 1996, and in 1998, the KFDSH was further elevated to the KFDA. With this change, the old regulations were revised, and new ideas to establish and improve the systems of clinical trials were introduced to keep pace with global trends. External factors such as the establishment of regional clinical trial centers (RCTCs) in 2004 and the Korea National Enterprise for Clinical Trials (KoNECT) in 2007 affected the development of clinical infrastructures, although in fact, several major regulation changes initiated by KFDA practically drove continuous growth of South Korea's clinical investigations.

Introduction of IND Opens a New World in Clinical Trials

Major changes in regulations were not limited to the Korea Good Clinical Practice (KGCP). KGCP harmonized with the ICH GCP in 2000 to aid clinical trial participants (sponsors and principle investigators) to carry out well refined investigation procedures. In 2002,

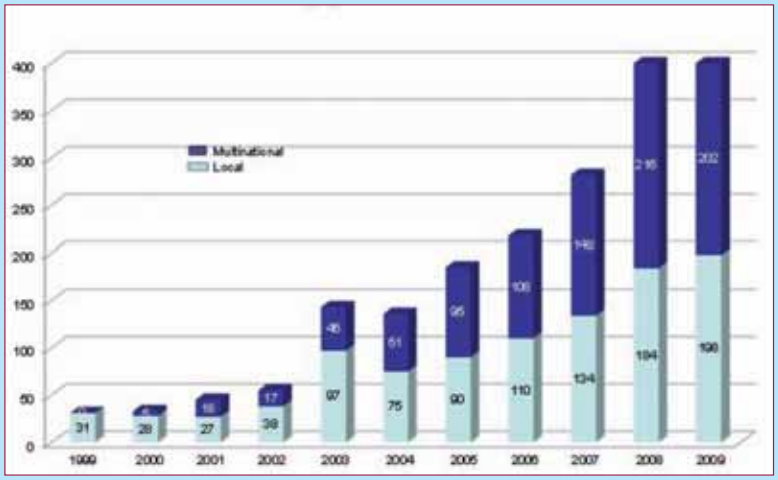


Figure 1. Annual report on the number of approved clinical trials

the Investigational New Drug (IND) approval, which separates IND and New Drug Application (NDA), was introduced. The IND applications in drug legislation allowed South Korea's institutions and clinical investigators to participate in multinational global clinical trials, and 55 clinical trials were registered in 2002. This number increased greatly, to 400, in 2009 (Figure 1).

QA of Clinical Trials

Furthermore, accreditation of clinical trial institutes by a regulatory authority such as KFDA, to assure the quality and capacity of the pool of institutes and qualified investigators with regard to their ability to carry out well refined clinical trials, was subsequently introduced. As of October 2010, regulatory authority-accredited clinical trial institutes numbered 142 for medicinal drugs and 81 for medicinal devices, most located in Seoul, followed by Busan and Dae-Gu (data not shown).

Inspection for Clinical Trials by KFDA

KFDA actively inspects, as a system-based approach, not only for NDAs but also sponsors, contract research organizations and institutions, including IRBs, during the clinical research period. The purpose of such regulatory-driven inspection is to enhance the quality and the competitiveness of clinical trials conducted in South Korea in order to secure the rights, safety, and welfare of subjects, since the new drugs and devices, not yet qualified with regard to their own safety and effectiveness, are used in human beings. Such clinical trials are the core of the development and approval of medical drugs and devices. Inspection is separated into two main forms, periodic (surveillance) and "for cause" (directed) inspections. Periodic inspections target sponsors, CROs, and accredited institutions annually to review their overall operations and the procedures of the IRB and/or sponsors, and to review the overall practice of investigators to make sure that every clinical trial participant

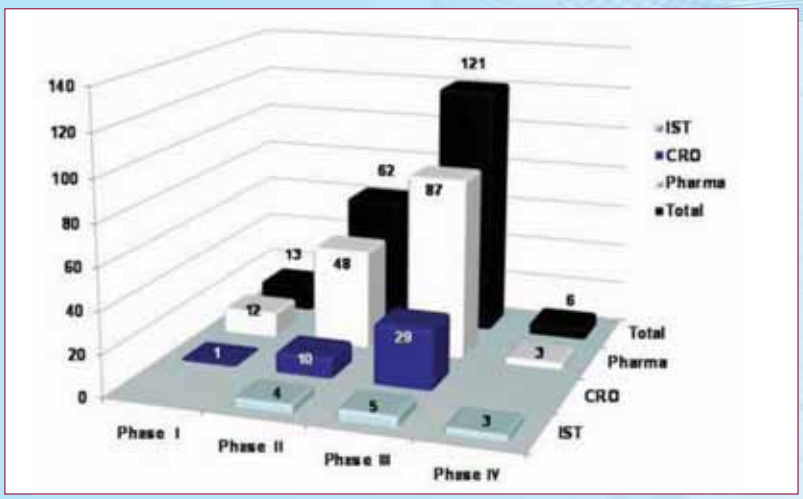


Figure 2. Multinational clinical trials in Korea, 2009 (CRO: Contract Research Organization, IST: Investigator-sponsored trials)

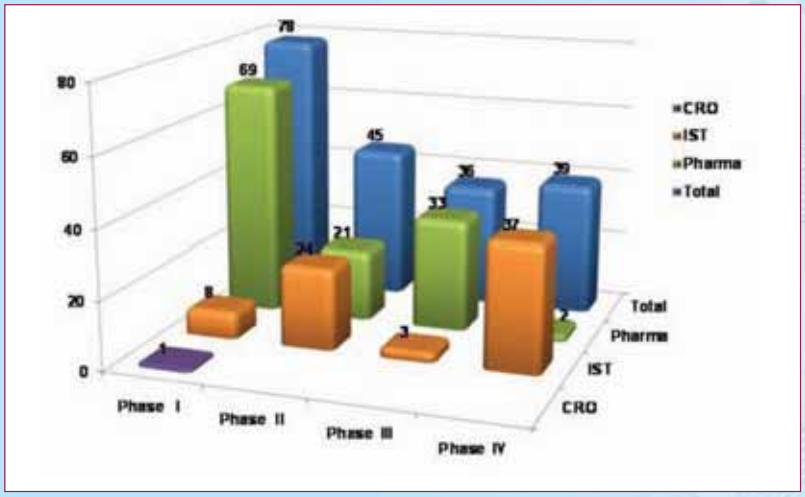


Figure 3. Local clinical trials in Korea, 2009

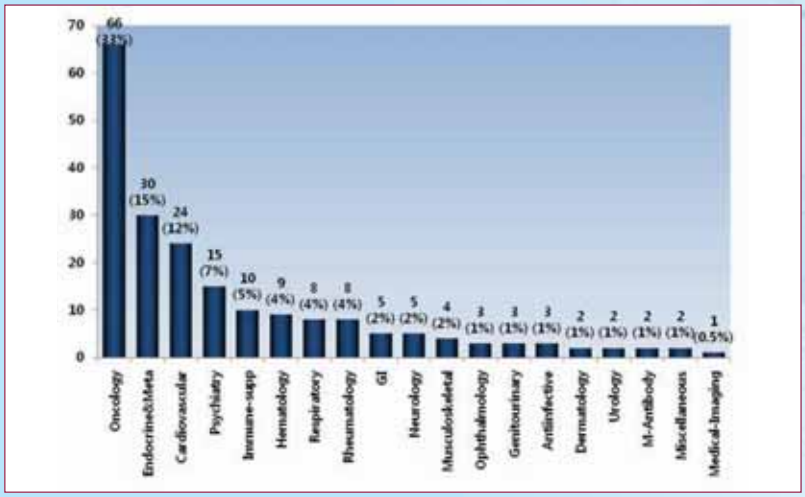


Figure 4. Therapeutic area of multinational clinical trials in Korea, 2009

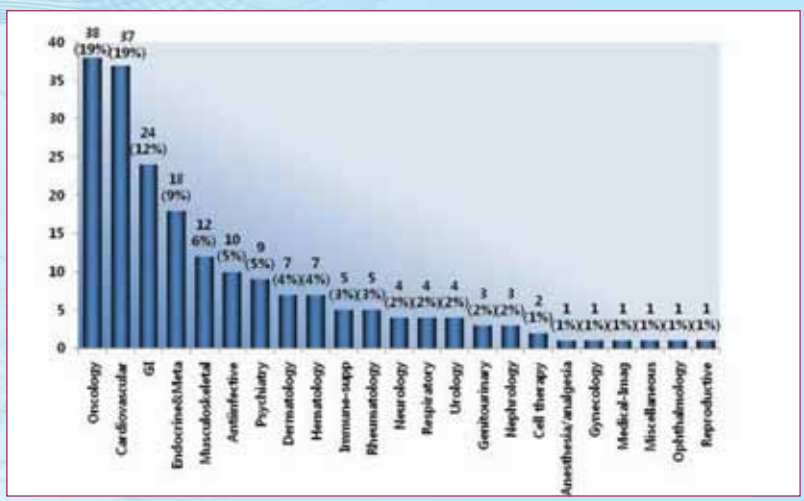


Figure 5. Therapeutic area of local clinical trials in Korea, 2009

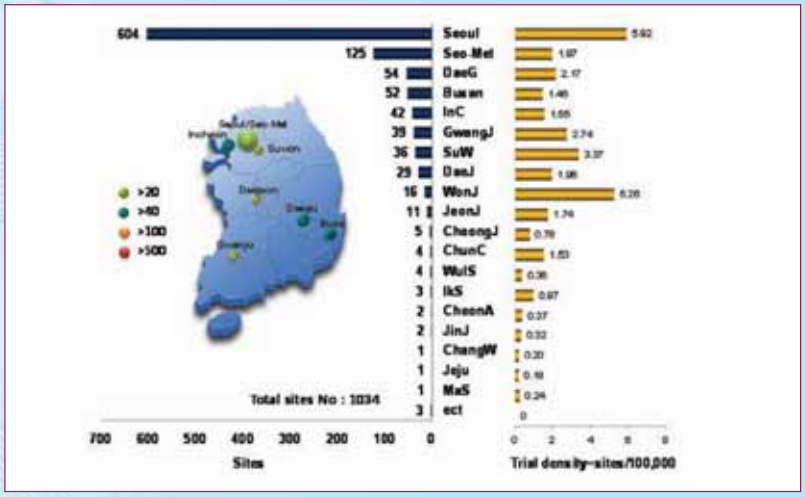


Figure 6. Geographic distribution of multinational clinical trials in Korea, 2009

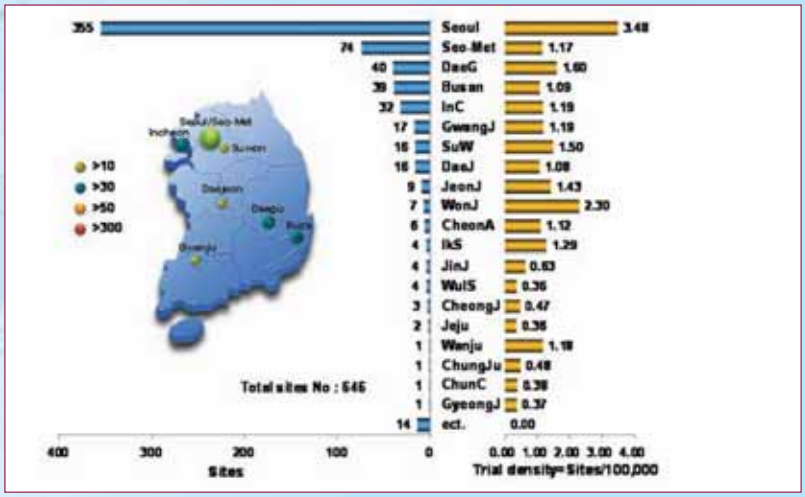


Figure 7. Geographic distribution of local clinical trials in Korea, 2009

conducts clinical trials according to KGCP. Directed inspections usually take place in the event of a death that qualifies as unexpected, when a suspected serious adverse event occurred during the trial, when there is an accusation, petition of corresponding clinical trials, or if KFDA is suspicious of the credibility of the study report. In 2009, KFDA inspected 24 sponsors (including 10 CROs) and 35 institutions nationwide for periodic inspections. There were also 27 directed inspections, including 11 inspections relating to a death, that same year.

Recent Changes and Improvements

Joint IRB

Because there has been a huge increase in large-scale clinical trials conducted in multiple institutions, every IRB located in every relevant institution in the conduct of multicenter trials was required to review the protocols and informed consents. To reduce such unnecessary duplication of review, expenses, and time delays, KFDA began to consider establishing a joint IRB, in which a result obtained by a central IRB for a particular protocol can be used and regarded as mutually approved by the other IRB. Although specified regulations and the IRB's own standard operational policies need to be further organized and improved to implement this cooperative IRB review model in clinical research, we think that the reduction in the number of needed IRB approvals may save time and reduce the work load for the local IRB.

Expansion of Accredited Institutes

The quality assurance of clinical trials was achieved through a system involving the accreditation of institutions by KFDA as discussed above. However, the main drawback related to accreditation of clinical trial institutes was found to be that it was hard to get relatively small institutions and private practitioners involved in conducting such regulatory-driven investigations. In addition, the majority of clinical

trials conducted in South Korea were held in the Seoul region. Such problems drove KFDA to introduce an amendment in 2008 to extend the regulatory policy to allow not only general hospitals but also special hospitals accredited by the Ministry of Health and Welfare, to become accredited after they successfully establish an appropriate facility, an IRB that consists of appropriate members according to KGCP, a pool of manpower to support the clinical trial, and laboratory equipment. (A "special hospital" is a hospital that is equivalent to a medical specialist training hospital.)

Establishment of Comprehensive Clinical Development Plan

We are now planning to implement a comprehensive clinical development plan by establishing a "2020 clinical future creation planning group" to set the direction for strengthening regulatory competitiveness and capability of clinical trials, building a safety protection system for subjects, constructing the enhanced communication system of clinical trials, and building a development plan for clinical trials of medical devices. We are expecting this initiative may lead South Korea to achieve the level of the five powers by 2020.

Competitive Reinforcement of Early-phase Clinical Trials

There is a point of view that the regulatory administration requires too much information for IND applications, previous to clinical trial initiation. One particular example could be a requirement of fully translated protocols in Korean, which in reality can take global sponsors quite a long time to prepare. This can certainly extend the time needed during overall drug development. For that reason, expansion of the workforce to include individuals who are qualified to review all the IND documents in English is also needed. On the other hand, many hold the point of view that the review period needs to be shortened. In fact, time is critical in the development phase, and therefore reducing the review period could be a favorable policy to adopt. Therefore, KFDA is considering the introduction of a new factor that acknowledges the importance of reducing the approval timeline for phase 1 trials that target healthy volunteers by half (from 30 to 14 days). However, in this case the pre-consultation with KFDA related to the corresponding drug must be completed. In addition, submission of protocols in English, as it is with translated protocol synopses, ICF, and compensation policy for victims in Korea, has been permitted since late 2010.

Introduction of International Safety Management System

Introduction of an international safety management system for concrete examples, such as annual reports according to ICH-E2F commitment for IND holders to KFDA and the IRB, preparation of well established guidelines for electronic data management in clinical trials, and enhancement of safety reporting requirements to IRBs are now being processed. Combined management of the accreditation process performed by KFDA for institutions for medical drugs and devices is currently being considered, since Korea has recently faced a large increase in the number and scale of clinical trials using such devices.

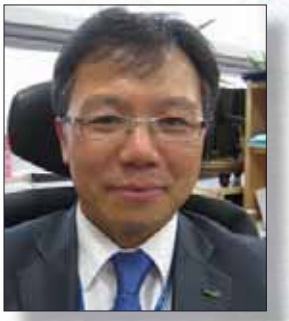
Conclusion

What we tried in the past and what we continue to do with clinical trials in terms of reformation and amendment of regulatory policies is the ultimate goal of our approach, in tandem with the desire to construct an advanced clinical trial system administration to increase competitiveness and establish a high-quality infrastructure for clinical trials in comparison with countries such as those in North America and Europe. We believe that our practices will protect the public health from undesirable disease and external pathogens more preemptively, promptly, and effectively and protect the rights, safety, and welfare of subjects during ethically conducted clinical trials to develop innovative new drugs for the market.

Methods

All the data represented in this article are from the statistical database analyzed by the clinical trial management division of KFDA. The numbers are based on the number of clinical trials and institutions registered between 1999 and 2009 in KFDA. ■

Min Jung Park



Young-Ok Kim

Yun-Hong Noh

Min Jung Park and Young-Ok Kim are part of the Clinical Trial Management Division, Risk Prevention Policy Bureau, Korea Food and Drug Administration, Seoul, Korea. Yun-Hong Noh is the Commissioner of the Korea Food and Drug Administration, Seoul, Korea.

OPERATIONS & BUDGETING-

a Primer for Clinical Trial Sites

Kimberly Irvine

These days, the clinical trial process is labyrinthine. Longer, more involved study protocols, enhanced IRB involvement, and more oversight by the FDA contribute to a research environment with unprecedented complexity.

However, there continue to be valid reasons to sign up as a clinical trial site: being at the forefront of research, building relationships with the pharmaceutical/biotech/device industries, providing opportunities to patients who are interested in clinical trials, building possible revenue streams, and developing staff expertise.

Each site needs to weigh the cost-benefit of participating in trials, and decide if they are willing to participate at a level that makes it worthwhile for them, their patients, and the study sponsor. As holds true in other aspects of life, study sites develop reputations for their conduct; it behooves them to weigh carefully their level of commitment and ability to see the study through to its conclusion in order to remain in good stead with the IRB, study sponsor, and CRO. Other decision points include: determining if the protocol is a good fit for the staff and patient pool, evaluating their ability to recruit and retain subjects, and ensuring patient protection.

Once these critical factors are determined, the more tangible elements of operations and budgeting must be addressed. Costs of conducting trials are on the rise, and per-patient reimbursements remain flat, so the ability to adequately budget and anticipate operational requirements is critical. Otherwise, sites that are ill-prepared in these areas will find themselves paying unanticipated costs that were not covered in the contracts, or being overwhelmed with the trial process itself – recipes for a frustrating experience and a likely boycott of participating in future trials.

Furthermore, a majority of research contracts require sites to agree to a holdback, ranging from 10% to 50%, depending on the type of clinical trial, to create incentive for sites to stay on track. However, if the study gets delayed for any number of reasons, milestone payments can be impacted, creating significant financial strain on sites that do not plan ahead.

To begin the budgeting process, the site needs to first gather the tools needed to generate accurate budgets: the study protocol, a budget spreadsheet, a schedule of study office hours, CRA visits, and investigator meetings, and the site's research fee schedule. Take into consideration the following additional costs and be sure to address them prior to the contract being finalized:

- Travel reimbursement and comfort items for study subjects (such as debit or gas cards, bus passes, blankets for warmth during lengthy office visits, office snacks)
- Costs to attend the investigator meeting (for investigator and study staff), including costs of bringing in temporary staff for coverage if the office remains open during the investigator meeting
- Administrative fees for office hours beyond the regularly scheduled times (some protocols may require patient appointments in the evenings or weekends)
- Staff time for completing study documentation, even after enrollment is closed
- Processing of significant adverse events documentation
- Off-site storage of study records, if the site does not have adequate space and the sponsor requires storage beyond the regulatory standard
- Other supplies as required by the sponsor (such as a dedicated refrigerator or cabinet for study drug)
- Any procedures that may require additional staff or a visit to a specialist
- Transportation support for patients who need assistance

Novice sites may be less inclined to ask for advance payments and interest for late payments, but once a site has established itself as a reputable, dependable location, these types of requests can be made to

lessen the financial burden on sites. Finally, "invoicing" can be a tool used to manage the work completed for a clinical trial as well as to document how much is owed by the sponsor or CRO. While many contracts do not require sites to send invoices, such an exercise helps the site to better manage their accounts receivable.

From an operational perspective, attention to detail is of paramount importance. There are additional items that help ensure smooth operations, safety precautions, and confer site protections, albeit not all required by specific protocols.

Evaluate current insurance levels. Sites may not realize that their standard insurance coverage does not include coverage for clinical trials. Additional cost may be adding malpractice and product liability insurance specifically for the purpose of research. This is an important topic to discuss during the site initiation visit, and determine if the sponsor provides indemnification from liability.

In the world of clinical trials, *staff turnover* is an unfortunately common phenomenon. Invest in educating and training of research staff to aid with retention. With a good understanding of the research process, the function of the IRB, human subject protections, the regulations, and research compliance matters, staff will be likely more satisfied with their research projects, rather than discontented in their role. Additionally, develop a personnel back-up plan in the event of staff attrition. In the absence of a study coordinator, for example, patient visits may be delayed, throwing the study timing into jeopardy as well as potentially impacting the data. It is a good idea to also cross-train office staff, in the event of absences. This way, activities don't come to a standstill if someone is out sick or on vacation.

The last topic under the subject of operations is the *ability to recruit study subjects*. This is the most critical part of conducting a study, yet it is the least understood and well executed. All site staff should be well versed in the study protocol, particularly the inclusion and exclusion criteria. Everyone can be an advocate and be able to address questions about the study. It truly is a team effort to bring appropriate patients into a study, requiring the investigator in particular to be involved, and not delegate communications to the office staff.

Recruitment can be achieved by advertising the study on posters and flyers in the office if the patient pool is part of the regular medical practice. If there is a need to go outside the practice and into the community-at-large, radio advertising can be effective, depending on the demographic of the target patient population. From newsletters to social media to bus shelter advertising - the options are numerous. These activities, of course, require funding, so be sure to discuss recruitment options with the sponsor/CRA to determine an adequate budget. For good input, speak to colleagues who have conducted studies locally – how did they get patients into the study? The take-home message here is to understand the role that active recruitment plays in bringing committed patients through the door. A passive approach is rarely successful – there are just too many obstacles and competing time commitments facing patients; it takes the study staff planning and focus to be successful.

Sponsors are generally not local, nor are the CROs. Taking responsibility for trial success falls squarely on the shoulders of every study site. They are the ones who know the patients and the community best. At any one time, large sponsors are running multiple trials involving hundreds, even thousands, of sites. CRA visits are sporadic, with more and more of them conducting site check-ins by phone and email. Therefore, each site must be self-sufficient and resourceful. Proactively anticipating the budgeting and operations pitfalls can save a lot of time and aggravation, and should result in a fruitful research experience for everyone. ■

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THE 3E PRINCIPLE OF OUTSOURCING

Chitra Lele and Larry Rothman

Drivers of outsourcing and influencers of partner selection vary on the basis of the imperatives and strategy of the sponsor organization and what is desired to be outsourced.

Reasons for outsourcing go far beyond labor arbitrage, which is considered the core reason most companies choose to use an outsourcing "partner." There are unprecedented shifts in the way biopharmaceutical companies conduct their business today, partially forced by macroeconomics, politics, population growth and aging, and the "flattening" of the globe, all of which provide previously unknown opportunities and challenges.

There is enormous pressure on the management of these companies to perform the concurrent miracles of significant cost reductions with simultaneous productivity improvements in order to thrive in their business. Drug discovery and development are becoming more complex and more resource intensive, despite increased automation. There are daily headlines of massive layoffs and facility closures. No corner of the business, regardless of the geography, is immune from these pressures.

As a consequence, the amount of outsourcing/out-tasking/off-shoring that the biopharmaceutical industry has undertaken has increased. While this industry has been late out of the starting blocks, the lost time is being rapidly made up. Variations on the theme are diverse and include captive centers, joint ventures with global outsourcing companies, major expansion of use of clinical research organizations (CROs), use of diverse geographies, and any other creative aspects companies can envision.

We outline three key areas of consideration for outsourcing, specifically in the context of outsourcing knowledge-based functions in drug development and postmarketing in the areas of safety and risk management, statistics and programming, and scientific writing. We call it "The 3E Principle" which encompasses the "whys" of doing business together. Each company's priorities differ, and the relative importance of these three principles in partner selection decisions also differs by the function that is being outsourced. The 3Es are Effectiveness, Efficiency, and Economics. We describe below what we mean by each of these.

Effectiveness. Effectiveness encompasses delivering quality and regulatory compliance, consistently and reliably. Given the volume, magnitude and variety of the functions and tasks involved, and the need to adapt processes to evolving regulations, it is a significant challenge for the sponsor company to comply effectively. Niche partners who focus on specific areas and make it their business to continually learn, adopt, evolve and comply, day after day, help realize the desired effectiveness.

Efficiency. Efficiency is defined as the ability to manage "peaks and valleys" in workload with minimal impact on productivity and cost. Specialized outsourcing partners provide just-in-time resources in fully outsourced or hybrid models.

Economics. Labor arbitrage is an important reason for outsourcing and off-shoring. Cost reduction without compromising quality and compliance is the key principle. The goal is to select outsourcing partners who absorb employee overheads, nonproductive time, etc, in a seamless manner, while maintaining the economic advantage.

Let us now analyze how "The 3E Principle" applies to each of the following service areas:

- Safety and Risk Management (SRM)
- Scientific Writing
- Statistics and Programming

Safety and Risk Management

Patient safety is clearly of paramount importance in drug development and marketing. Regulatory reporting compliance is critical for each reportable adverse event and each aggregate safety report. Compliance with company SOPs is also extremely important. The pharmacovigilance function tends

to be most scrutinized by regulators, and any noncompliance is likely to lead to serious consequences. Changes in the drug development process, globalization, and the dynamics of collaboration in the biopharmaceutical industry lead to evolving regulations for safety reporting in many regions of the world. Hence, subject matter expertise and ability to be on top of changing regulations is a key requirement for sound pharmacovigilance operations. Hence the first "E," ie, effectiveness, is often a driver for outsourcing and thus is a mandatory requirement of any outsourcing partner.

For a mid-to-large-size pharmaceutical company with a sizable portfolio, the impact of volume fluctuations on resource needs is not high. Process and productivity improvements are expected on an ongoing basis given the nature of the business, and these are important. Overall, however, efficiency ranks lower than effectiveness as part of the decision to outsource and vendor selection.

In our experience, cost reduction is a major consideration for mid-to-large pharma companies when they decide to outsource safety operations, especially postmarketing spontaneous reporting. Though the entire SRM was considered to be a CORE function until a few years ago and hence was retained in-house, with the increasing pressure on R&D productivity and cost reduction, companies are now interested in outsourcing safety operations and retaining the strategy in-house. They find ways of minimizing the risk in outsourcing, for example, by outsourcing only the data entry part of single case processing while retaining triage and medical review with themselves, or outsourcing a subset of cases (eg, literature cases) where the risk and impact of failure are low.

Small companies that have only a select set of products, on the other hand, tend to be highly risk averse since they have so much at stake with just one or two molecules that they are developing. However, they also don't have the wherewithal to set up safety operations in-house. Thus, they are forced to outsource, but they tend to outsource to established near-shore providers rather than selecting the option of offshore delivery. Cost reduction isn't as important a consideration for such companies.

For the risk management part of SRM and for other safety activities that are resource intensive but also require significant domain expertise (eg, writing periodic safety update reports and performing signal identification and analysis, running patient registries as part of Risk Management Plans), effectiveness and efficiency feature higher than economics when outsourcing decisions are made.

The 3E Matrix (Hierarchy of Relevance of the 3 Principles)

	Mid-to-Large-Size Companies	Small Companies
Safety Operations	Effectiveness	Effectiveness
	Economics	Efficiency
	Efficiency	Economics
Risk Management, Other Safety	Effectiveness/Efficiency	Effectiveness
	Economics	Efficiency
		Economics
Scientific Writing	Efficiency	Effectiveness
	Economics	Efficiency/Economics
	Effectiveness	
Statistics and Efficacy Programming	Efficiency	Effectiveness
	Effectiveness	Efficiency
	Economics	Economics
Safety Programming, Mapping	Economics	Effectiveness
	Efficiency	Efficiency
	Effectiveness	Economics

Scientific Writing

We define scientific writing as comprising safety writing (aggregate reports, etc), clinical writing (clinical study reports, protocols, IBs etc), regulatory writing (sections of CTD involving clinical/nonclinical overviews and CMC manufacturing changes, as well as Integrated Summaries of Safety and Efficacy) and preparation of medico-marketing literature (such as product toolkits, product-specific and therapeutic area-specific training for sales and marketing personnel and manuscripts for publications).

Although there are some differences across different categories of writing, for scientific writing as a whole, the primary driver for outsourcing work is the need to have adequate resources available when required (in order to deliver on regulatory reporting compliance or any other deadlines). Achieving compliance is challenging, primarily from a resourcing consideration rather than due to evolving regulations. Thus, efficiency is the main driver for outsourcing of scientific writing work and is a major criterion for partner selection. In today's environment, economics comes in second ,and effectiveness is the third principle that plays a role.

Statistics and Programming

Though it is natural to combine statistics and programming, the drivers for outsourcing statistics tend to be quite different from the drivers for outsourcing programming work. We define statistical services as comprising statistical contribution to study design, planning, oversight, and conduct of the statistical analysis of clinical trial and any other related data. For the purpose of this discussion on outsourcing, we could segregate programming into safety programming and mapping on one hand and efficacy programming on the other hand.

Due to the increased focus on making trial designs more efficient, the requirement for statistical resources has increased significantly. At the same time, due to acquisitions and portfolio rationalization, both the peaks and valleys get accentuated in the context of statistical services. The regulators come out with new guidance documents in order to provide some direction to the industry about new statistical methodology required to make design and analysis more efficient. This implies that the statisticians performing the outsourced work have to keep abreast of all new guidelines on an ongoing basis and need to have good subject matter expertise. The volume, and hence budgets, for outsourcing statistical work are quite low, so cost reduction doesn't feature as a major driver for outsourcing these activities. Thus, we believe that efficiency is very important, with effectiveness coming in at a close second and economics trailing behind the other two principles.

The primary consideration for outsourcing domain-intensive efficacy programming work is similar to that for outsourcing statistics work, so efficiency is the most important principle that is applied when decision to outsource such work is made and vendors are selected. However, the outsourcing budget for programming tends to be higher than for statistics, since the volume of work and number of resources required are much higher. Thus, effectiveness and economics are about equally important.

The volume of work involved in safety analysis and mapping data between standards is higher for mid- to large-size companies than for small companies. At the same time, large companies tend to have established libraries of programs and macros that can be used repeatedly. Hence, economics tends to be the primary driver for the selection of a provider for outsourcing. Efficiency is the second most important consideration, since the peaks and valleys apply equally to safety programming and efficacy programming and statistics. Effectiveness would rank third among the 3E principles.

For small biopharmaceutical companies that typically don't have statistics and programming capability in-house, effectiveness ranks at the top for outsourcing decisions, with efficiency coming second, and economics in the third position. There is no differentiation across statistics, efficacy programming, and safety programming in the case of these companies. ■

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ICH at 20
AN OVERVIEW

Betty R. Kuhnert, Section Editor

If you've been in any area of the pharmaceutical industry for even a short period of time, you've probably heard of ICH. You may think of ICH as one or more of the specific guidelines that relate to your function in the industry (ie, in clinical E6 (GCP); in data management, M1 (MedDRA); in regulatory M4 (the CTD – Common Technical Document), etc). However, equating ICH to its guidelines is like the blind men trying to describe an elephant where one feels the trunk and says the elephant is like a snake, and the one feeling a leg says the elephant is like a tree trunk. ICH is much more than the sum of its 50 final guidelines.

ICH stands for The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Its mission is: "To achieve greater harmonization to ensure that safe, effective and high quality medicines are developed and registered in the most resource-efficient manner." The key term is "resource-efficient." Since its beginning in April 1990, ICH has worked to harmonize the criteria and documents required for approval and authorization of new medicinal products. Benefits include preventing duplication of clinical trials, minimizing the use of animal testing without compromising safety and effectiveness, and streamlining the submission preparation and regulatory assessment processes. The result is to reduce development times and resources needed for drug development and ultimately to facilitate the access of patients to new, safe, and effective drugs.

Originally, ICH consisted of representatives of the regulatory agencies and industry associations of the three ICH regions, Japan, the US, and the European Union. In addition, representatives from other countries such as Canada, and the World Health Organization were present as observers and were quick to support the ICH initiatives. The key to success was the commitment of the ICH regulators to implement the final guidelines, and attention was directed towards facilitating the implementation of ICH Guidelines in ICH's own regions. Entering into the third decade of activity, ICH is now also focused on extending the benefits of harmonization beyond the ICH regions and involving regulators in non-ICH regions in guideline development. To further this initiative, a Global Cooperation Group was formed that has become an important subcommittee of the Steering Committee. Many other drug regulatory authorities worldwide have chosen to implement some or all of the ICH guidelines in their regulations. For example, the article in this series by Justina Molzon focuses on the relationship between the Asia-Pacific Economic Cooperation (APEC) and ICH.

The areas selected for harmonization were divided into safety, quality, and efficacy because these were the criteria that are the basis for approval and authorization of new medicines. If a topic doesn't fit cleanly in one of the categories above, it would be put in the M or Multidisciplinary category. Accordingly, the guidelines produced by ICH, are designated by the letters E, Q, S, or M: Efficacy guidelines, such as E6 (GCP) and E3 (Clinical Study Reports), are concerned with the design, conduct, safety, and reporting of clinical trials. Quality guidelines, such as Q7 (GMP) include harmonization achievements in the areas of stability studies, defining relevant thresholds for impurities, etc. Safety guidelines, such as S1 (Need for Carcinogenicity Studies), include a comprehensive set of guidelines related to carcinogenicity, genotoxicity, and reprotoxicity. The article by Jan Willem van der Laan later in this series provides an interesting personal perspective on what it really took for harmonization related to the S1 guideline to occur. Multidisciplinary guidelines include ICH medical terminology (MedDRA, M1) and the CTD (M4). All together there are about 80 guidelines and annexes in the four categories that are either final or in various stages of development. The guidelines are guidelines and not regulations; thus, they are intended to be used in combination with regional requirements.

The ICH has also been working to facilitate international electronic communication through its Electronic Standards for the Transfer of Regulatory Information (ESTRI).

A result of this has been the Electronic Common Technical Document (eCTD), which allows for the electronic submission of the CTD from applicant to regulator. The article in this series by Nancy Katz discusses some of the competencies regulatory writers need to work effectively with the eCTD.

Early on, the benefits of ICH efforts were mostly to industry because harmonization reduced the duplication of testing and reporting necessary for submissions to multiple regulatory agencies. However, there are immense value and benefits of ICH to regulators as well. The CTD and the eCTD have revolutionized how submissions are reviewed. They have created a common regulatory language that promotes good document review practices and ultimately leads to faster access to life-saving medicines, even beyond the ICH regions. ICH has shifted its emphasis from the input of information by industry to the output of information by regulators, a transformation only made possible by the CTD. The CTD has also made the exchange of information among drug regulatory authorities easier. This is addressed in the articles in this series by Françoise de Crémiers related to E3 and how it led to the CTD, and the article by Yves Juillet on the CTD as a tool for global development and assessment.

The best place to learn more about ICH is the ICH website (http://www.ICH.org). There you can find information about the history and organization of ICH, how the process of harmonization actually works, and get answers to frequently asked questions such as how you can get involved in the process. I would recommend reading the publication found there entitled, "The Value and Benefits of ICH to Drug Regulatory Authorities – Advancing Harmonization for Better Health." This article salutes two decades of ICH's groundbreaking work in harmonizing drug regulatory requirements among many global partners. Included are articles about how the guidelines are implemented, information about the eCTD, the impact of ICH in Japan, and more information about the ICH's Global Cooperation Group, which is described as a "Bridge from ICH to the World Beyond." There is also material about guideline information/dissemination in non-ICH countries, and a list of ICH guidelines finalized as of July 2010.

Gone are the days when loading the hundreds of volumes of paper documents for a submission to a given country on a truck and watching it go down the road, was an excuse for a party before the effort began all over again for submission to the next country. Today, it doesn't take six to nine months or longer to reformat the documents for the next submission. Also gone are most of the clinical studies done for one specific country. Instead, global clinical trials and bridging studies (E5) allow extrapolation of foreign clinical data to new regions. Thanks to ICH and improved technology, the process has gone from multiple paper submissions for various regions to a much more resource-efficient, common, standards-based, electronic submission and review process.

The articles that follow highlight some of the main contributions of ICH over the past 20 years. It should not come as a surprise that three of the five relate to the CTD, since M4 has revolutionized how submissions are prepared and reviewed. The article by Françoise de Crémiers focuses on the birth of E3 (Clinical Study Reports) and how its development led to the CTD. The article by Yves Juillet focuses on the CTD as a tool for global development and assessment. The article by Nancy Katz focuses on competencies needed to produce an eCTD. The article by Jan-Willem van der Laan discusses the challenges and personal satisfaction of being part of the ICH safety initiatives. And finally, the article by Justina Molzon alludes to the increased globalization of pharmaceutical development and the APEC regional harmonization initiative. ■

References

ICH
http://www.ICH.org

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We had planned to include an article offering the Japanese perspective on harmonization as a part of this section. However, the recent tragic events in that country prevented us from securing the article. We hope to be able to include this article in a future issue.

ICH
harmonisation for better health

THE BIRTH OF ICH E3 AND HOW IT LED TO THE CTD

Françoise Augier de Crémiers

The concept of harmonizaton supported by ICH procedures and guidelines was the outcome of informal discussions that began in 1987 - 1989 between Europe, the US, and Japan. The need for harmonization was first addressed at the International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989. An ICH preparatory meeting was held in 1990 in Brussels with Dr. F. Sauer (European Commission), Dr. Nelly Baudrihaye (EFPIA), Dr. Shirota (JPMA), Dr. Osuma Doi (MHW), Professor J.M. Alexandre (CHMP), Dr. E. Esber (FDA), and A. Jaquinto (PhARMA), establishing the preliminary ICH framework. These architects were the builders of the ICH process, which provided for true collaborative development of international guidelines between drug development experts and regulators from the three regions.

The concept, the procedure with the different steps, and the guidelines to be selected were decided at the first ICH conference held in Brussels in November 1991. The ICH E3 guideline (The Structure and Content of the Clinical Study Report) was one of the first topics selected, along with the ICH E6 guideline (GCP). ICH E3 was the first step aimed at harmonizing the clinical documentation of drug development, and resulted in the harmonized clinical study report. The topic was officially selected in March 1992, and the final ICH E3 guideline was implemented in the three regions in 1995/1996. The highly motivated ICH E3 expert working group was created in 1992 and was initially under European leadership until step 2 was achieved. At that time, computers and IT support were not effective enough, and the secretariat was supported by US and EU industry resources. This assistance was of the utmost importance for the review process by the three regions' experts during the ICH working meetings and intermediate consultation periods.

It should be noted that the three regional medical writers' associations also played a significant role in the development of the E3 guideline. They brought to the table practical experiences through forums such as DIA workshops that allowed exchanges of views between drug developers and regulators. These discussions brought to light potential pitfalls as well as positive items. Their participation was greatly appreciated and facilitated the ICH E3 implementation through changes to international company SOPs so that they would be applicable for a clinical study performed in any of the three regions and later Canada.

Parts of the clinical study report guideline were based on the US Food and Drug Administration (FDA) guideline entitled Format and Content of the Clinical and Statistical Section of New Drug Applications – July 1988. The statistical part of the clinical study report closely resembles the FDA guideline, with certain modifications. However, after extensive initial comparative analyses and evaluations, the FDA guideline underwent significant changes to take into account ethical requirements and to make it compatible with EU, USA, and Japanese regulations. The ICH E3 guideline also took into consideration the different regional Health Authority approaches and philosophies regarding drug assessment.

The "modularity principle" was applied. A common core format allowed preparation of a worldwide core clinical study report that would be acceptable to all Regulatory Authorities. This core clinical study report was to be completed with appendices. Each appendix was to be considered as a separate module, meeting specific regional regulatory requirements, depending on the three regions' regulations. Taking the principle of modularity into consideration, the core report and appendices could be separated. This approach would avoid unnecessary duplication, and waste of resources and time. A common format would not only benefit the industry, but

potentially also allow patients faster access to new medicines.

Although the intended scope of the ICH E3 guideline was to cover pivotal efficacy and safety studies, the basic principles and structure described could also be applied to other areas such as pharmacokinetic/pharmacodynamic studies. The ICH E3 guideline was to be used in conjunction with other ICH guidelines dealing with efficacy and safety.

Subsequently, worldwide industry surveys were conducted by PhRMA to find out how long it took to convert a registration dossier prepared in one region for submission to another region once the drug development process was complete. The results presented to the ICH Steering Committee were based on recent experiences from eight different companies and showed that ten months were needed to convert a US/NDA into an EU/MAA! This was the starting point for the ICH Steering Committee's decision to set up the ICH CTD expert working groups. Different groups addressed the different parts of the registration dossier related to quality, safety (nonclinical), efficacy, and multidisciplinary topics.

Thus, the success of ICH E3 led to the birth of the ICH CTD efficacy expert working groups. Continuity with the previous expert working group was ensured by involving Dr. R.Temple and Dr. F. de Crémiers, who had been involved with E3. The ICH CTD-efficacy guideline was intended to harmonize the structure and format (or table of contents) of the clinical part of the "common" registration dossier in order to benefit from standardized sets of tables, tabular overviews, and tabular listings. The modularity principle was again applied to allow for regional requirements. Moreover, guidance documents regarding an overall written clinical summary, as well as an executive summary, were prepared. These allowed "unique" summaries providing identical information and formatted in the same way that as a result, could be submitted simultaneously to the three regions and Canada. Modular appendices for specific regional requirements still remained, such as the US Integrated Safety Summary. Global companies could provide this document in the EU submission as an appendix referenced in the Table of Contents.

In conclusion, the ICH E3 guideline and the ICH CTD efficacy guideline have proven to be acceptable, standardized formats for the preparation of global clinical submissions. The modular formats have saved time and resources, and have greatly facilitated early access to new innovative medicines. In addition, the common formats have facilitated discussions and exchanges between drug developers and regulators, and have led to better dialogue in terms of public health needs for the patients. ■

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THE CHALLENGE AND SATISFACTION OF GLOBALIZATION

A Personal Perspective

Jan Willem van der Laan

Globalization in the regulatory field of human medicines cannot be discussed without the important initiative of the ICH, a short abbreviation for a long name: International Conference on Harmonisation of Technical Requirements for Medicines for Human Use.

This name also defines the boundaries: only technical requirements, not the language. Whether it is "harmonization" or "harmonisation" is not important.

First Experience: Carcinogenicity

In January 1992 I got the chance to participate in the ICH process by joining the Carcinogenicity Expert Working Group at their first meeting in Whitehall in London. The topic of carcinogenicity is complex, consisting of different aspects such as dose selection and a possible discussion of the relevance of the two individual rodent species.

This first process revealed differences in thinking between the various geographic areas, including the representatives who attended the meeting. The representatives from Japan (Ministry of Health, Labor and Welfare, MHLW) and the USA (FDA) consisted of a battery of experts, including at least one carcinogenicity expert. In addition, the FDA had just started the Carcinogenicity Assessment Committee to achieve consistency across divisions in their decisions regarding carcinogenicity study protocols and interpretation of results. In Europe, however, the individual (national) nonclinical-assessment groups were (and still are) rather small. Therefore, my first task was to learn about the main issues in carcinogenicity testing. With a huge number of papers in my suitcase, I started my career with ICH.

An important factor in the ICH was the interaction between industry and regulators as equivalent partners. The input from industry prevented the regulatory parties from being too theoretical in their requirements, leading to real discussions about how to assess safety for humans. On the other hand, industry was asking for detailed guidance that might eventually be too prescriptive, preventing thinking by the industrial experts themselves.

Globalization is multidisciplinary. Defining the need for carcinogenicity studies required that clinical expertise be brought into the group when we discussed the duration of clinical treatment for patients. Contact with the clinical experts at ICH was easy in the so-called Caucus meetings taking place during ICH meetings.

Globalization should be data driven. The FDA had conducted an overview of the ratios in exposure of rats versus humans for a series of pharmaceuticals. This database clearly showed the limitations of having a general requirement of a range of exposure of animals over humans. It showed also that the use of extremely high doses (because of low toxicity) was limited. A variety of endpoints had to be defined, such as the maximum tolerable dose, the maximum feasible dose, the exposure-based maximum dose (with the factor 25), and a few others.

The issue of species choice led us to build a database in Europe. A problem in Europe was the lack of a central administration, as the European Medicines Agency (EMA) was not yet established. Therefore, we decided as a Dutch group to cooperate with Germany.[1] This database taught us a lot about the value of the carcinogenicity studies in the pharmaceutical field, ie, that the contribution of mouse studies to carcinogenic evidence was low, although we had to admit that the relevance of the rat studies was also rather low. After having reached agreement in general terms under the excellent chairmanship of Lars Ekman, a Swedish representative of the pharmaceutical industry, most of the time was spent on the text of the guidance documents.

One specific moment is worth mentioning. We had just finished the document on the Need for Carcinogenicity Studies (S1A), with a short preview of the next decade announcing the use of transgenic animals. We then started with the next document, the Choice of Species (S1B), and the FDA representative

proposed including the possibility of using transgenic mice. From a European viewpoint, I would reduce the requirements to one species, the rat, being unhappy with these mice. I explicitly indicated that this position would be not acceptable for the EU. The FDA representative could also not handle this situation, and started reading a newspaper. At that time, the chairman announced a break in the meeting. During this break, emotions settled down, and the discussion on transgenics was deferred to a later stage. As a result of this meeting I was invited by the FDA representative to join the FDA for a month, and to spend a month at his home. The MEB (Medicines Evaluation Board) sponsored my flight. I became a temporary FDA employee, and this was a great experience.

Globalization leads to friendship. My work with my host Joe DeGeorge, led to a lasting friendship. I had also the opportunity to meet several pharm-tox colleagues from CDER and CBER, which was important for the future work in ICH.

Globalization brings about cooperation: ICH, HESI, and DIA.[2] The discussions in ICH led to a new global initiative, within ILSI (International Life Sciences Institute)-HESI (Health and Environmental Science Institute) located in Washington, DC, to evaluate transgenic and other models. This project was important and led to encounters with the challenges in the ICH process. DIA played an important role in this process, by taking the opportunity to organize a meeting discussion in Noordwijk in 1997 on "Alternative Models in Carcinogenicity Testing."

This first experience in globalization was challenging because of the different issues in the field, but very satisfying as changes in the strategy for testing drug safety could be initiated, and more importantly as friendships resulted from these intense discussions.

Second Experience: Immunotoxicity

Globalization should be data driven. Another challenge was the topic of immunotoxicity. The process started in our institute in the 1980s, where strategies to detect immunotoxicity were developed for environmental chemicals such as tributyltinoxide (TBTO) under the leadership of the late Sjef Vos. The Safety Working Party (SWP) invited him in 1989 to introduce immunotoxicity in the pharmaceutical arena, but the topic required more data. In the early 1990s, the Medicines Evaluation Board supported a program to validate an approach in immunotoxicity by conducting animal testing with a range of pharmaceuticals. These studies were led by Eric de Waal and Henk van Loveren. At the same time, my own research was on opiates, because of questions about their immunosuppressive potency in drug abusers infected with HIV.

Globalization should be led by scientific discussion. When all these studies were finished and most of the data were published, a process was started to bring this topic into the global regulatory environment. A DIA workshop in January 1995 in Arlington, VA, was devoted to this topic. One day was spent on immunotoxicity in close cooperation with immunotoxicologists in the US and especially within FDA (Ken Hastings) and NIEHS (National Institute on Environmental Health Sciences) (Mike Luster). An explicit driving force was Jack Dean. In Arlington, it became clear that the time was ripe to extend the topic. Therefore, another DIA workshop was held in 1996 in Montreux, resulting in recommendations. This was an important step in the globalization of this topic, as leading immunotoxicologists from the US and Japanese pharmaceutical industry participated.[3]

Despite these workshops, the strategies of the different regulatory parties were different. The EU incorporated a paragraph on immunotoxicity testing in their Guideline on Repeated Dose Toxicity finalized in 2000, whereas the FDA released their first draft document in April 2001, and a Japanese draft document was published in December 2001.

Soon after the publication of these guidances, the issue of immunotoxicity was brought to the table at ICH. In November 2001, a third DIA workshop was organized again in Noordwijk in the Netherlands to discuss the situation. The conclusions of this meeting were published in the *Drug Information Journal*.[4]

Globalization should be data-driven. In February 2002 the different approaches were discussed in Brussels, but it was decided just to gather data, and to continue to learn from experience in the pharmaceutical industry. We spent nearly two years on this. In July 2003, we proceeded by analyzing the database in Brussels. Despite the small amount of data, we decided to proceed and to ask the industry for more input in the meantime. Eventually the survey

contained 45 compounds. Only six were positively scored as immunotoxic in functional tests without being positive in other respects.[5] At that time an important realization was that the European request for routinely conducting immunotoxicity studies might be regulatory overkill. This recognition brought into play the possibility of harmonization of this topic between the various regions. *(Globalization may be painful.)*

The final point can be briefly stated: the challenge was to maintain the most important aspects of the immunotoxic risks in the documents, without overemphasizing the need for functional screening.

From this second experience we again learned that guidance documents have to be based on sound data, and harmonization can be reached only through further analysis of the way things work in industry. It is important that in the field of toxicity testing of human pharmaceuticals, companies will take some risk by conducting studies.

Third Experience: Regulatory Language and Safety Testing of Biotechnology-derived Proteins

In 2006 the SWP was asked to evaluate the existing guidelines and to think about the possibility of adding new issues to the ICH list of topics. On behalf of the SWP, I wrote a short notice, and we made a list of topics as a proposal for a brainstorming meeting.

The brainstorming discussion took place in June 2006 in Yokohama with a rather straightforward outcome. It was chaired by Professor Tohru Inoue, representing the Japanese authorities who were hosting the meeting, and by me, representing the initiator, the EU. The following were among the many topics that were discussed.

Globalization is accepting differences in legislative culture. The topic that was expected to be a quick-win, ie, a very small revision of S1C took 18 months with legalistic discussions with FDA, turned out to be a nice learning experience. There is specific regulatory language that is sometimes difficult to understand. As a non-native speaker I learned that "warranted" is not a commonly used word in the American and English language. However, it is commonly used to express that a certain test is needed or "called for." But since the discussion on the S1C, we have a list of "unwanted" words, which apparently express a requirement or statement too strongly. For example, the word "acceptable" is not acceptable, and the word "appropriate" is more appropriate, unless we really believe that a certain approach is acceptable. It might be difficult to accept that a certain region might be so dominant in the character of the wording, but in fact that is one of the challenges in harmonization… to accept the legalistic approach of one of the parties. In the same way, the US parties have to respect the opinion of the EU that the use of animals should be reduced as much as possible.

Another outcome of the brainstorming session was the request for revision/updating of the Guideline on Preclinical Testing of Biotechnology-derived Proteins. It was, however, decided that this revision could be done only after evaluation of the experience gathered thus far. This decision was an important aspect of the process.

It was therefore important to organize regional meetings to discuss the evidence available at that time on the different topics that needed to be harmonized. In Europe, together with the EFPIA Safety Group and the Immunotoxicity Summer School, we organized a day in Lyon to discuss the "hot items," eg, the duration of chronic toxicity studies, reproduction toxicity, immunogenicity, and carcinogenicity.

Together with a student, I took the challenge of the reproduction toxicity studies for this type of compound. This led us deep into the differences between human and animal placental physiology.[6]

Other datasets were gathered on the character of chronic toxicity, tissue cross-reactivity, and carcinogenicity of biotechnology-derived pharmaceuticals.

As a whole, the process was very satisfying in this respect, as all of these reviews have substantially improved the knowledge of regulatory experience in this field.

Globalization is respecting each other's way of organization. The process of updating/revising the S6 Guidance is close to being finalized, as we have been waiting a few months for final agreement among the pharm-tox assessors of the FDA. This might be frustrating sometimes, but that's all in the game, and therefore it is a challenge.

Other Experience: World Health Organization

Globalization is involvement with developing countries. The ICH is not the only organization with a global impact. In fact the WHO has an older tradition. My involvement is in the

vaccine field, as the institute where I am working has held an important role with respect to vaccines since the first half of the 20th century, when it developed the national vaccination program for children. The character of the work for WHO is different, as the lead is more in the organization itself, in this case in the Unit for Biological Standardization. Meetings organized by WHO are bigger than the Expert Working Groups in ICH, and more multidisciplinary in design. In most cases there is explicit representation from the developing countries, which are hardly present in ICH. Also, the topics in the vaccine field are different and more applied to specific types of products, such as plant vaccines, DNA vaccines, and malaria, dengue, and yellow fever vaccines. From that point of view, the work is very satisfying since it is influential in the daily life of developing countries.

One of the challenges in the WHO vaccine field is the introduction of the ICH system of the Common Technical Dossier. The development of a vaccine requires a close interaction between the biotechnological process of the production of a vaccine, and the proof-of-concept testing or safety testing. The differentiation between master seed, working seed, and final lots is very important in the vaccine field and is not always easy to compare with the different stages of development of a common human pharmaceutical. From that point of view it is also not easy to make a strong distinction between Module 3 (Quality part) and Module 4 (Nonclinical testing part) of the CTD. Testing of neurovirulence (translated as central nervous system toxicity) belongs to the testing of the master seed or working seed, in the common human pharmaceuticals part of early development, whereas testing the safety of local tolerance should be conducted with the final product, ie, the first final lot. It is a real challenge to harmonize these types of principles.

Personal Globalization

Globalization is experiencing brotherhood. Traveling around in the world is a challenge as such, meeting people in different cultures, in different environments and with their own specialties. For me an additional value is meeting and experiencing brotherhood with people all over the world.

Conclusion: Globalization is a challenge in various respects, but gives a high level of satisfaction.

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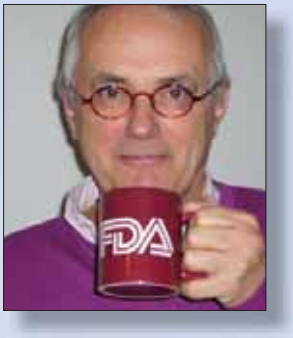

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THE CTD A TOOL FOR GLOBAL DEVELOPMENT AND ASSESSMENT

Yves Juillet

Harmonization is not an objective as such. The aim of this activity is to create a substantial uniformity between the requirements in different regions to facilitate the access of patients to new drugs. It should limit unnecessary delays in drug development and also avoid animal and human study duplications. In doing that, it saves regulatory authorities and industry both time and money.

When the ICH process started in the early 1990s, only harmonization of the dossier content was considered. At that time it was not even conceivable to think of harmonization of the format. The first success of the ICH guideline implementations made this project possible.

At the end of the 1990s, when the work started, the objectives of the CTD were clearly stated:

- Reduce the time and resources needed to compile the applications for different regulatory authorities
- Make preparation of the file easier
- Facilitate regulatory reviews and communication between authorities and applicants
- Facilitate the exchanges of regulatory information between authorities. (Harmonized numbering allows easy reference to the same part of the dossier.)

CTD Definition and Reality

The CTD has been defined as an agreed-upon common format for registration applications. In theory, it was not concerned with the content. In practice, the development of the CTD project required a lot of effort to verify that the words had the same meaning in the three ICH regions (and they did not). This exercise then led to a thorough review of the content of the registration dossier. This review was needed to clearly identify each part of the CTD (granularity) to allow for harmonized numbering.

Even more difficult was the harmonization of the application summaries. The word "summary" did not have the same meaning, nor did the sections have the same length, in the different regions.

What Has Been Achieved?

Ten years after implementation, it is possible to clearly state that the CTD has been a success. It is now totally adopted in the three ICH regions, even if there are slight differences. In practice, these differences are limited to a few paragraphs. The main differences are still the length of the summaries and the remaining requirement in the US for the ISS (Integrated Summary of Safety).

It is interesting to note that during the CTD implementation phase there were no major changes, only very minor ones, and it was adopted easily by regulatory authorities and industry.

The review process was also made easier for both regulatory authorities and the day-to-day work of assessors, showing that the logic behind the development of the CTD was correct.

Thanks to its robustness, it has been possible to develop an eCTD, whose objectives go far beyond the simple electronic submission, and include facilitating the review process itself.

It is interesting to note that one of the main aims, "To facilitate the exchange between regulatory authorities" has been a real success, as evidenced by ongoing regular contacts between regions regarding topics such as pharmacovigilance and scientific advice. This is not a surprise for Europeans, who knew that the European registration system only started to emerge when the European format and the expert reports were finalized and adopted.

The data are impressive. In December 2009, less than 10 years after the CTD launch (ICH San Diego 2000), the US FDA processed its 100,000th eCTD !

The CTD as a Global Tool

The CTD was initially developed by ICH for the ICH countries/regions.

Some additional countries, ICH observers (Canada, Switzerland), and Australia immediately adopted the format.

A major step towards globalization was taken in 2004, when the Regional Harmonization Initiatives (ASEAN, APEC, GCC, SADC and PANDRH) led to invitations to regulatory authorities from different countries such as China or India to become members of the ICH Global Cooperation Group. This quickly led to a better understanding of the ICH process and results.

Even when not always formally implemented, the CTD is now present in most of the regions.

It is clear that the CTD, which allows for a better global understanding of regulatory requirements, has helped these countries not only to develop their own registration processes, but to participate more and more in the development of new ICH guidelines.

The CTD is also the tool that is clearly used by emerging countries to attract industry sponsors to place clinical trials in these regions. It is now impossible for these countries to play a key role without adopting the ICH guidelines, including the CTD and Good Clinical Practices.

In addition, it allows the regulatory authorities to develop contacts and cooperation among the different agencies, in particular with the most stringent authorities.

The CTD, an Easily Adaptable Tool

Often compared to a pyramid, the CTD is composed of modules and submodules. Each part could be compared to stones or bricks.

The composition of the dossier would not be the same if a new compound or generic were considered. For generics, only some parts of the CTD are required: Module 1 (administrative information), Module 2 (Summaries), Module 3 (Quality part), Module 4 (usually not necessary), Module 5 (usually limited to bioequivalence studies).

It seems clear that regulatory authorities in different parts of the world have neither the same needs nor the same means. They often don't need all the stones, nor are they able to use them. Even in the least developed countries, the use of the CTD Module 2 (summaries) will help authorities to get needed information and will allow them to question agencies in more developed countries.

It is interesting to see that the harmonization initiative, which has just started in Africa, is clearly based on the use of the CTD. The CTD is now considered the common ground on which the different countries/regions will be able to build their own harmonization activity little by little.

When the CTD exercise started, the question was: "Will the CTD save time and money?" The answer is clearly "yes" and much more. It has allowed all stakeholders from the different countries to be and to stay on the same page. It is now the adopted and indispensable framework for all regulatory activity from development to marketing, while still allowing for regional variations in ICH and non-ICH countries.

The CTD is a success story led by a few people who were optimistic enough to make things happen despite the difficulties and conservatism present within both industry and the regulatory authorities at the time. It will be the basis for further harmonization activities. ■

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EFFECTIVE eCTD WRITING
FIVE ESSENTIAL COMPETENCIES[1]

Nancy R. Katz

How does a writer effectively create documents for a drug submission based on the Common Technical Document (CTD), and in particular, a CTD that will be submitted electronically (an "eCTD")? This article describes five essential competencies that enable the delivery of eCTD-compliant documents.[2]

- An understanding of the rationale for the CTD: standardization, transparency, and effective reviews.
- An understanding of the structure (pyramid and Greek temple) and content of the CTD, as well as of the individual documents that comprise the CTD.
- The ability to create regulatory-compliant, scientifically accurate, linkable, clearly written documents, which, taken together, contain consistent messages that contribute to the case for drug approval.
- The ability to reuse content.
- Finally, and not altogether incidentally: the ability to get along with others and work as part of a team.

An Understanding of the Rationale for the eCTD: Standardization, Transparency, and Effective 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 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" (www.ICH.org).

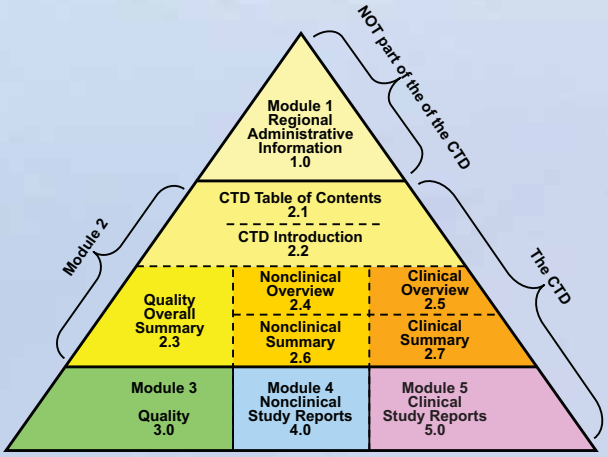
A drug application submitted in CTD format supports the goal of ICH by eliminating redundant applications: one CTD-based drug application can be submitted to and accepted for review by regulatory agencies in any country of each of the three ICH regions. An electronically based application (that is, an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

1. Portions of this article were published in Your Career as a Biopharmaceutical Regulatory Writer in Choosing the Right Regulatory Career, edited by Peggy J. Berry, 2010; RAPS and The eCTD and beyond: a primer for regulatory writers. DIA Global Forum; 2010; April:16-21.
2. For a thorough discussion of competencies for medical writers, many of whom write eCTD-compliant documents, see Woolley KL and Clemow D. Development and use of an international medical writer competency model. DIA Global Forum; 2010; June: 8-11.

trace the reasoning and data upon which the scientific conclusions of the application are based.

An Understanding of CTD Structure and Content: 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 graphic was created as a slide for a DIA presentation by Christopher Preston and is reproduced with his permission.)

This is a most useful way to conceptualize the CTD; the next sections examine the pyramid 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.

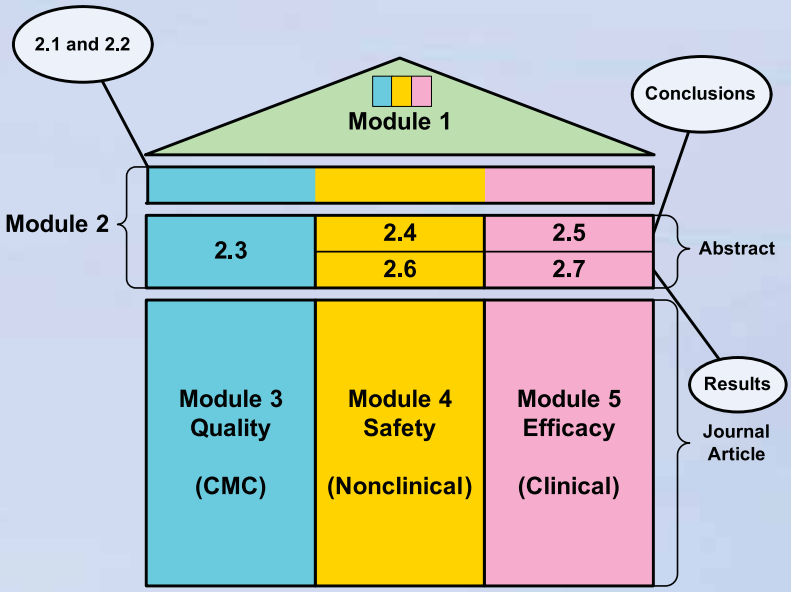
(Some nomenclature is useful at this point: Regulatory writers who write the documents for Module 3 and 4 are sometimes called *technical writers*. Those who write documents for Module 5 are often called *medical writers*. But this distinction is blurring fast, and is not always useful. A writer who 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 (nonclinical 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 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.



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

The Ability to Create Regulatory-Compliant, Scientifically Accurate, Linkable, Clearly Written Documents, Which, Taken Together, Contribute to the Case for Drug Approval

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.

a) Regulatory-compliant, scientifically accurate documents:

Competencies that allow achievement of this standard include knowledge of the following:

1. Regulations and guidelines governing the relevant documents in the CTD submission (Please contact the author for this information.)

2. 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).

3. 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).

4. 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).

5. 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.

b) Linkable documents: More and more, regulatory authorities worldwide are expressing a preference for electronic submission of CTD-based drug applications. To comply, the regulatory writer must ensure that any document created as part of a submission 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.

c) 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 thorough understanding of the efficacy and safety of the drug, 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.

d) Consistent messages: A message, in regulatory parlance, is the translation of quantitative data into a *valid* qualitative statement. To the best of your ability, ensure that any message in any document you create is a valid message. For example, if you write, in the discussion section of a clinical study report, that the drug "is well tolerated in the patient population tested," ensure that the statement can be backed up by summary tables of adverse events as well as data in individual patient listings. Be sure also, that the same message (with supporting data) appears in the Clinical Overview (Section 2.5), the Summary of Clinical Safety (Section 2.7.4), and the Integrated Summary of Safety (Section 5.3.5.3). And especially make sure that the message hasn't evolved into something inaccurate such as "this drug is safe for anyone and everybody." (No joke, drift like this happens.)

The Ability to Reuse Content

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) employing sophisticated software that allows direct access of approved "topics"

into the document a writer is creating. 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: The Ability to Get Along with People and Work as 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 ("messages," discussed above); circulates documents for review; adjudicates comments from colleagues; and finalizes a document for publication into an electronic format. In addition, the writer performs less glamorous tasks: ensures that abbreviations are used consistently throughout all documents; indicates, often by using blue font, which text needs to be linked to another part of the document, or another document in the submission; and ensures consistency of voice throughout the submission (eg, does your sponsor say "in the opinion of the Investigator, the drug contributed to a clinical benefit for the patient" or "The Investigator judged the drug to benefit the patient"? It is certainly true that "a foolish consistency can be the hobgoblin of little minds" (Ralph Waldo Emerson, *Self-Reliance*, 1841); however, an intelligent consistency certainly promotes ease of reading and timely reviews.

The writer also realizes that team review may result in re-conceptualization of the structure and content of a document, and that consequently, that writer may have to revise the document from the ground up. (For example, just imagine that at the last minute the sponsor changes the indication for the drug from "therapy for patients with moderate asthma" to "therapy for patients with mild-to-moderate asthma," and envision the changes the writer must make.)

A successful document for eCTD submission depends on the writer's willingness to get along with and learn from others and, when necessary, engage in ego subordination and/or intelligent assertiveness. For instance, a reviewer may insist that a well cadenced sentence crafted by the writer be turned into a grammatical but awkward piece of prose; in this case, the writer is silent. On the other hand, if the sponsor considers 20,000 pages of text an acceptable Summary of Clinical Safety, that writer is responsible for diplomatically and firmly pointing out that the guidance for that section specifies a much lower limit. 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 any writer who wants to be part of an eCTD submission team.

In addition, the writer who writes eCTD-compliant documents must keep in training. A writer should regularly perform a gap analysis, identifying areas that impede his or her ability to function (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

The eCTD is here to stay. A drug application in eCTD format enables efficient reviews by regulatory agencies, which in turn allow faster delivery of new medicines to those in need. A writer participates in this effort by creating scientifically accurate, clearly written, eCTD compliant documents. Such a writer will always be a valued member of a drug development team. ■

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APEC AND EFFORTS FOR REGULATORY HARMONIZATION

Justina Molzon

Introduction

The Asia-Pacific Economic Cooperation (APEC) is a forum for Pacific Rim economies to promote economic cooperation throughout the Asia-Pacific region. It was established in 1989 in response to the growing recognition that the Asia-Pacific region had numerous comparative and complementary advantages. APEC's goal is to raise living standards and education levels via sustainable economic growth and to foster a sense of community and appreciation of shared interests among Asia-Pacific countries. It does this by promoting trade, sustainable economic growth and prosperity of member economies through policy alignment and economic and technical cooperation.

APEC currently has 21 members, including most countries with a coastline on the Pacific Ocean.

This article will describe how recent developments within the APEC Life Sciences Innovation Forum (LSIF) are important in advancing a more strategic, coordinated and sustainable approach to regulatory harmonization and cooperation among medical product regulatory authorities.

Background

APEC is a unique forum operating on a basis of nonbinding commitments, open dialogue, and equal respect for views of all participants. Decisions are by consensus, and commitments are on a voluntary basis.

At APEC meetings held at Los Cabos, Mexico in October 2002, APEC Leaders endorsed a proposal to establish the Life Science Innovation Forum (LSIF). This reflected the belief that life sciences innovation was important in promoting the improvement of both public health and economic development in the APEC economies. Perceived as an annual forum, LSIF would serve to promote policy discussion and projects aimed at advancing life sciences innovation. From the outset, harmonization was seen as a prerequisite to promoting innovation and a key element of robust health systems .

LSIF was well positioned to serve as an enabler of harmonization as its role was not to produce harmonized documents, such as ICH, but to promote the use of existing international guidelines. Participation in LSIF was voluntary, and this ensured participation of those economies interested and committed to cooperation and harmonization. Further, APEC funding was available to advance proposed projects focused on harmonization and a series of workshops on anti-counterfeiting, clinical trial evaluation, and Good Clinical Practices (GCP) inspection and ICH Quality guidances were offered throughout the APEC region.

APEC leaders also endorsed the development of a strategic plan to address health challenges and economic development goals. The strategic plan was to include identifying factors critical to success in each segment of the life sciences value chain. The resulting strategic plan was endorsed in November 2004 and led to a focus on implementation projects in priority areas, including harmonization.

It was felt that regulators were a critical component of the life sciences innovation critical path and that the

APEC Members

Australia
Brunei Darussalam
Canada
Chile
People's Republic of China
Hong Kong, China
Indonesia
Japan
Republic of Korea
Malaysia
Mexico
New Zealand
Papua New Guinea
Peru
The Philippines
Russia
Singapore
Chinese Taipei
Thailand
The United States
Viet Nam

effectiveness of a regulatory authority in fulfilling its mandate is critical to the achievement of desired life science outcomes. APEC leaders recognized the importance of good regulatory performances and harmonization in contributing to life sciences innovation.

This consideration is illustrated by elements of the LSIF Strategic Plan:

- Harmonization of standards… according to international best practices… will give the APEC region a competitive edge and expand opportunities for the rapid development of innovation

- To maximize the region's ability to address the region's health needs policies, standards and regulatory mechanisms should be reviewed against international best practices, in accordance with APEC principles on harmonization.

APEC's focus on harmonization emphasized that there should not be a duplication of efforts and that where international standards exist they should serve as the basis for harmonization throughout the region. Further, where appropriate organizations exist for developing international standards, APEC economies should promote the development of international standards through these bodies.

Despite these efforts, it was recognized that LSIF was not being used to its full potential in promoting a more strategic and effective approach to regulatory harmonization and cooperation throughout the APEC region. As a result, in August 2008, a series of strategic discussions took place during the LSIF VI meetings held in Lima, Peru, and a separate regulatory session was held to examine the potential of LSIF to promote the achievement of regulatory harmonization in the region.

This session was attended by medical product regulatory authorities, industry, academia, and contract research organizations from the APEC region. Speakers helped frame the discussion by sharing views on the importance of international exchange and technical cooperation, internationally harmonized standards, the ICH Common Technical Document, and the WHO's regulatory assessment tool in promoting Good Regulatory Practices, and the possibility of leveraging regulatory resources.

Recommendations from this meeting to the APEC LSIF included:

- Establishment of the APEC Harmonization Center to address regional regulatory priorities

- Assessment by member economies of current regulatory capacity and resource levels as an important step in determining appropriate regulatory strategies and models, including the adoption of harmonized standards

- Working toward adoption of harmonized application and compatible review formats to promote a common regulatory language that supports sharing of information, good regulatory practices, and leveraging of resources

- The need to conduct a feasibility study on the confidential exchange and use of regulatory information

- The formation of a regulatory steering committee composed of interested economies.

These recommendations led to the establishment, with support from South Korea, of the APEC Harmonization Center (AHC) and the creation of a Regulatory Harmonization Steering Committee (RHSC)

The APEC Harmonization Center

At the 20th APEC Ministerial meeting held in November 2008 in Lima, Peru, the AHC was endorsed by the APEC ministers.

> "Recalling our commitment to promoting regulatory reform and harmonization, we welcomed and endorsed the establishment of the APEC LSIF Harmonization Center in Seoul as a key step forward. "

With the establishment of the APEC Harmonization Center in March 2009, a formal mechanism was in place to enhance and sustain the implementation of harmonized standards and regulatory best practices throughout the APEC Region.

The AHC goals are to:

- Support access to the best practices and guidelines for regulatory harmonization

- Promote collaborative actions and information exchange

- Promote the conduct of clinical trials that meet international standards

- Enhance the quality, safety, and efficacy of therapeutic products.

The AHC serves as an APEC-wide resource for capacity-building efforts by conducting research and surveys, providing educational programs, publishing outcomes of meetings and trainings, and establishing networks and exchanges between participants and relevant international institutions.

The Regulatory Harmonization Steering Committee

The Regulatory Harmonization Steering Committee (RHSC) was created to promote a more strategic, effective, and sustainable approach to harmonization by proactively identifying and prioritizing projects seen to be of greatest value and providing direction to the AHC on projects and activities that best meet these needs. The RHSC in partnership with the AHC will establish or strengthen linkages with other harmonization initiatives, training organizations, and key players in efforts to promote complementary actions and the most effective use of limited resources. These activities are to be conducted in accordance with an overall strategic plan and roadmaps focused on medical products (pharmaceuticals and medical devices).

The RHSC Work plan for 2010-2011 includes a series of workshops targeting the following priority areas:

- Multiregional Clinical Trials (MRCT)
  - MRCT/Tripartite Symposium (pharmaceuticals),
  - Medical Device Clinical Trials,
- Good Review Practices and the exchange and use of regulatory information
  - Pharmaceuticals,
  - Medical devices
- Global Harmonization Task Force Implementation,
- Pharmaceutical Quality
  - Integrity of the Supply Chain
  - ICH Quality by Design Workshop
- Pharmacovigilance
- Stem Cells (prospective harmonization)
- 6th Pan-Asian Regulatory Conference (IFPMA/DIA/AHC)

An example of how AHC and RHSC work together to accomplish their objectives may be found in the MRCT Workshop held in Seoul, Korea in June 2009. This workshop served as a "diagnostic" of MRCT challenges, issues, and opportunities in the APEC region. The workshop provided a series of recommendations to address the challenges of conducting MRCT. These recommendations were considered in developing APEC project proposals that could lead to concrete directed in support of overall harmonization goals. As a result, the second workshop on MRCT was conducted in September 2010 to drill down into the issues and concerns delineated in the first program to get to their root cause and provide for possible pathways to successful MRCTs in the region. Many Ministers have endorsed the achievement of regulatory harmonization, thus demonstrating strong political support.

Conclusion

Recent developments in the APEC have implications beyond the region in advancing regulatory harmonization in a more strategic, sustainable, and effective manner. APEC RHSC and AHC activities are being seen as playing a key role in building a better global harmonization model.

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Justina Molzon, MS Pharm, JD, CAPT. USPHS, *serves as Associate Director for International Programs, CDER, FDA.*

DIA, AHC, & IFPMA will co-sponsor the 1st Asian Regulatory Conference: Asia's role in Global Drug Development, April 26-28 in Seoul, Korea. See page 60 for more on this conference.

PROFILE OF

ZHANG WEI: GLOBALIZATION IS A "DOUBLE-EDGED SWORD"

Interview conducted by Mao Donglei,
Medicine Economic News

In recent years, more and more multinational pharmaceutical companies have established R&D centers in China that are participating in simultaneous global development. What are the opportunities and challenges that simultaneous global development brings to the new drug review process in China? How do reviewers in China evaluate their capacities and levels of drug review and approval? Recently, Medicine Economic News held an exclusive interview with Mr. Zhang Wei, Director of Drug Registration Department, State Food and Drug Administration (SFDA). Zhang Wei elaborated on the critical stages of drug innovation, simultaneous global development, and the review timeline, and also gave a brief review on the evolution of the criteria, regulations, and concepts for drug registration in China.

Q&A Hello, Director Zhang. In the past decade, pharmaceutical R&D has promoted the transfer from a "me-too" strategy to proprietary innovation in the pharmaceutical industry in China. Good social benefits have been achieved, and some innovative drugs have been launched in the market. What are the favorable factors for R&D and innovation in China currently?

Promoting innovative drug development is a national policy. Globalization of pharmaceutical R&D promotes the transfer from "me-too drugs" to proprietary innovation in pharmaceutical R&D in China. China's pharmaceutical R&D has five advantages: First, government's focus on medical innovation is increasing. Second, significant progress has been achieved in intellectual property protection of pharmaceutical products. Third, infrastructure of the pharmaceutical industry in China is relatively well equipped. Fourth, the segmentation and support of the pharmaceutical industry in China have been streamlined. Fifth, China has rich human and clinical resources. The pharmaceutical innovation system, with the cooperation of industry, academia, and R&D in China, has been formed progressively with the promotion of the government, enterprises as the undertaking subject, R&D institutions as the support, and the market as the orientation.

However, there is still a certain gap between China and developed countries in pharmaceutical R&D, particularly in pharmaceutical innovation. One important point is inadequate R&D investment, which has a direct impact on the improvement of new drug R&D capacity and innovation.

Q&A With the introduction of various innovation incentives, pharmaceutical companies in China are now faced with unprecedented opportunities to narrow the gap with pharmaceutical companies in developed countries and to make innovation the promoter for the pharmaceutical industry in China. From the view of the drug regulator, which improvement measures have been taken to encourage innovation?

In updating the regulations, SFDA has promulgated and has implemented the revised Provisions for Drug Registration from October 1, 2007. Amendments of the Provisions for Drug Registration are based on the following three principles: First, to encourage drug innovation, to guide R&D of generic drugs in China, and to contain low-level drug applications by focusing on technology to improve the threshold for drug application. Second, to solve the key problems of unmet medical needs to realize clinical values and clinical advantages. Third, to establish a fair, transparent, and effective review system, strengthen the responsibility

division and power control, rationally allocate reviewing resources, and improve the review mechanism and procedure to realize openness and transparency as much as possible.

In addition, based on the current situation of innovative drug R&D in China, we issued the Provisions for the Administration of Special Examination and Approval for the Registration of New Pharmaceuticals. It is expected that the focus on innovation in chemical structure only in chemical drug innovation while neglecting clinical value as in the past should be shifted. Currently, disregarding the value of clinical research is one of the important reasons why the markets for some Class I novel drugs are difficult to expand. In addition, there are risks in clinical trials for some new drugs, and these risks cannot be eliminated by relying on review. They should be managed through risk management plans implemented by the sponsors.

In supporting global pharmaceutical R&D, some improvement measures were also introduced. For example, the timeline for technical review of a new drug clinical trial application has been shortened by 25%. We also accept applications according to ICH-CTD format; requirements for submission of cGMP certificates have become more flexible; and the review process for preclinical testing for the imported drug has been simplified.

Q&A You have just talked about globalization of pharmaceutical R&D, which has become a necessity, the shift of the focus of the value chain of pharmaceutical R&D to China has become a trend. How can we understand globalization, and particularly simultaneous global development (SGD)?

With the rapid development of China's economy multinational pharmaceutical companies have developed a great great interest, and are looking forward to making good use of the advantages in cost, human resources, and patient pool in emerging countries such as China and India to accelerate new drug R&D, expand the target market, and lower R&D cost. However, due to the high risk of new drug development, many companies have to move forward cautiously. If China can use its political system to advantage, acceleration in the establishment and implementation of effective policy advantages will no doubt make China move ahead in technology development and capital introduction for drug innovation.

Globalization is actually a "double-edged sword." For drug regulators, "globalization" not only brings opportunities, but also severe challenges. For simultaneous global development, we have the following views and understanding:

First, as one of the key components of globalization, simultaneous global drug development has come to Asia, particularly to emerging markets.

Second, global drug development brings challenges to drug regulators in emerging markets. We need adequate resources and scientific review capacity to ensure high-quality completion of drug reviews, and to make rational judgments and decisions within appropriate timelines. At the same time, we should maintain consistency in decision making and speed up the progressive integration with international standards and management regulations.

Third, global drug development also brings challenges to drug regulators in mature markets. With more and more clinical trial data from emerging markets, regulators in mature markets are faced with the same problems as we are in China, namely how to support local marketing applications with clinical data collected from other countries or regions. Thus, we think that exchanges and cooperation of regulators in emerging and mature markets will be closer in the future.

Fourth, global drug development also poses challenges to pharmaceutical companies. With the continuous improvement of the technical review capacity of drug regulators, pharmaceutical companies, particularly multinational pharmaceutical companies are asked to treat emerging markets not just as bases for clinical trials. In the meantime attention should be paid to the training of the local drug regulatory staff in both their scientific capacity and communication ability. Not paying attention to such kinds of capability building may lead to an extension of the review timeline.

Q&A As drug regulators in emerging countries, particularly as a regulator in China, how can we actively respond to the challenges of globalization and continue to develop effective management approaches to better protect the public health?

Here, I'd like to share a view of Dr. Murray Lumpkin, who is the deputy commissioner at FDA. When talking about international coordination, he believes that it does not mean completely copying drug regulatory policies and identical practices. As long as countries share a scientific basis and foundation, then they can operate uniquely according to their respective national conditions.

In general, "more dialogue and less confrontation, more cooperation and less blame" should become the mainstream for pharmaceutical regulators in emerging markets and mature markets to respond to global pharmaceutical development, strengthen cooperation, and achieve win-win. Simultaneous global development is a new task for drug regulators in China. "China is ready" should not be a simple, empty statement, but should be an approach to be implemented.

Q&A Industry is very concerned about review timelines for drug regulators in China, and review quality and efficiency are common challenges faced by drug regulators in various countries in the world.

Indeed this is true. Factors affecting review timelines are complex and diverse. But there is a misunderstanding that should be pointed out. In the past, we tended to consider that extended review timelines were a problem of SFDA alone. We can see that, according to the relevant requirements in the newly revised Provisions for Drug Registration that took effect from October 1, 2007, drug technical review in a drug evaluation center takes 90 working days; and administrative review by the SFDA takes about 30 working days. Therefore, under normal circumstances, it takes about 120 working days for the clinical trial of a new drug to be approved.

However, many people may not notice that, in the review process, our provisions provide a Request for Evidence (RFE) procedure. Once the RFE procedure is initiated, the time for pharmaceutical companies to answer questions from drug regulators and to prepare a variety of information shall not be included in the review timeline. If a pharmaceutical company neglects the training in the scientific capacity of regulatory staff, the preparation of application materials may be unscientific and inadequate, or the questions asked by drug regulators may not be answered on time, and the actual review timeline will be greatly extended. Therefore, drug regulators should pay attention to review timelines In addition, pharmaceutical manufacturers should check their internal procedures, and whether a review timeline is extended or not is attributed to the pharmaceutical manufacturers themselves. This is one of our points of view.

In general, drug review and approval is an interactive process, which requires communication, exchanges between reviewers and applicants, and the use of valid data and rational views to convince the other party. Only by active cooperation of both parties in accordance with the law can maximum efficiency can be achieved.

Q&A In retrospect of the past, despite the many achievements in drug registration and administration in our country, problems and insufficiencies are apparent. What would you like to say about the challenges we face in drug registration and administration, particularly in encouraging innovation?

After years of rectification and improvement, consolidation, and standardization of R&D institutions, manufacturers and registered products, pharmaceutical R&D has been greatly improved. However, we are still concerned about the clinical trial field, which involves many problems, and thus we deal with it very cautiously.

The positive factors for the promotion of clinical trials can promote the improvement of pharmaceutical R&D in our country, get more R&D investment, and the corresponding administration rules and system can be promoted and improved accordingly. However, from the perspective of the national macro-management, the balance of interests of domestic industry and foreign industry must be handled properly. The opening of a clinical trial will lead to the influx of drugs made by foreign manufacturers, and a series impacts on the utilization of clinical resources, market sharing, the public's access to originators' drugs, and pricing differences of patent and generic drugs. All of this should be considered and responded to by drug regulators. ■

DIA Introduces the HIMSS Interoperability Showcase℠ at DIA 2011

HIMSS Interoperability Showcases℠, traditionally held at HIMSS conferences at locations around the globe, are unique events where stakeholders come together to demonstrate the benefits of using standards-based interoperable health IT solutions for effective and secure health data information exchange.

This year, DIA, in cooperation with the Clinical Data Interchange Standards Consortium (CDISC) and Integrating the Healthcare Enterprise (IHE), is pleased to announce the debut of the HIMSS Interoperability Showcase℠ at DIA 2011. This Interoperability Showcase will feature cutting-edge technology and standards in an interactive environment that simulates how health information is seamlessly passed from care providers to facilitate clinical research and safety reporting. These demonstrations, held on the exhibit floor during exhibit hours, will use standards from CDISC and HL7, enabled by integration profiles from IHE, and will follow story lines that illustrate the flow of data from electronic health records to research systems.

Participating vendors will be required to conform to the standards-based approaches, and to test against other vendor participants to ensure a smooth, successful demonstration. Prior to the opening of DIA 2011, a testing event (in IHE terms, a "Projectathon") will be held. This formal testing process will test each vendor's compliance with the standards and profiles that enable the interoperability. We expect to have observers from FDA and ONC at both the Projectathon and Showcase.

The Showcase demonstration will feature a Research Information Exchange (RIE) with network services provided by vendors. EHR systems will provide access to clinical data and to the processes that enable protocol execution at sites. EDC vendors will demonstrate forms management and data capture. Additional specialized services such as eSource archiving, business process orchestration, redaction services, and identity management, will also be demonstrated.

Attendees will experience the services on the research information exchange through guided tours that follow specific story lines. These stories enact use cases such as regulated clinical study, drug safety reporting, and devices adverse event reporting. Each use case will demonstrate how the participating systems provide services which, taken together, create the research information exchange.

Please direct any questions to Landen Bain at lbain@cdisc.org. ■

Landen Bain

About Our Collaborators

HIMSS is a not-for-profit organization exclusively focused on providing global leadership for the optimal use of information technology (IT) and management systems for the betterment of health care. Serving over 30,000 members and 450 corporate members, HIMSS frames and leads health care practices and public policy through its content expertise, professional development, and research initiatives designed to promote information and management systems' contributions to improving the quality, safety, access, and cost-effectiveness of patient care. Visit them online at www.himss.org.

CDISC is a global, open, multidisciplinary, nonprofit organization that has established standards to support the acquisition, exchange, submission, and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of health care. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC website. Visit them online at www.cdisc.org.

IHE International and IHE USA are global nonprofit entities that enable the collaboration of health care providers and industry leaders to work together to improve interoperability and exchange of health information. IHE utilizes a proved framework for standards-based interoperability of health care IT systems which is being adopted and implemented worldwide. Visit them online at www.ihe.net.

What's New at the Annual Meeting: Expanded & Consolidated SESSION TRACKS

The saying, credited to Anthony Robbins, goes, "If you always do what you've always done, you'll always get what you've always got."

But you'll see that nothing could be further from this truth than DIA 2011, which will offer new educational formats – including forums, workshops, and webinars – alongside topics presented in more traditional and familiar Annual Meeting sessions. Simultaneously, the educational content in numerous tracks has been expanded, consolidated, and streamlined, to focus on the hottest topics among perennial and emerging business and regulatory strategies and processes.

Nonclinical & Early Clinical Translational Development, and **Regulatory Affairs & Sciences, Quality & GxP Compliance,** are two of DIA 2011's "new" and yet familiar Annual Meeting educational tracks. Representatives from the committees that chair these two tracks shared these perspectives on the new visions for these tracks with the *Global Forum.*

The Nonclinical & Early Clinical Translational Development Track is chaired by Paul Brown, PhD (FDA); Cecil Nick, MS (PAREXEL Consulting); Frank Sistare, PhD (Merck & Co., Inc.); and Howard Uderman, MD (Pfizer, Inc.). *Drs. Brown and Sistare collaborated on these responses.*

Paul Brown

Frank Sistare

Q&A What new, expanded, or different topics are included in this year's Nonclinical & Early Clinical Translational Development Track that might have been part of a different track, or perhaps not even addressed at previous Annual Meetings?

The Nonclinical and Early Clinical Translational Development Track has merged topics from the areas of nonclinical, preclinical and biotechnology, which were previously covered in separate tracks. This allows the integration of some areas for which there is significant overlap. Meeting attendees will benefit from hearing discussions on such cross-cutting topics as biomarker development, translational development of patient-specific medicines, and how clinical needs drive nonclinical testing.

Q&A You have provided leadership to this track for several Annual Meetings. In what other ways has this track grown and changed during this time?

The track has evolved to provide a stronger link between the clinical and nonclinical realms of drug development and to erase some of the artificial boundaries that have existed between biotechnology and "traditional" pharmaceuticals.

Q&A In your opinion, how do these changes reflect new and changing industry and regulatory dynamics in 2011?

The new track better reflects current industry and regulatory dynamics. The regulation of biotechnology and other pharmaceutical products has become more harmonized with a greater emphasis on the similarities of these technologies rather than the differences. Industry has also moved toward a more integrated approach in the development of these products, and this is reflected in both scientific and business changes in the pharmaceutical industry.

The Regulatory Affairs & Sciences, Quality & GxP Compliance track is co-chaired by John Aitken, PhD (Gilead Sciences); Roy Baranello, MS (ViroPharma Incorporated); Fritz Erni, PhD; Chin Koerner, MS (Novartis Pharmaceutical Corporation); Elaine Morefield, PhD (FDA); Joseph Scheeren, PharmD (Bayer HealthCare Pharmaceuticals, Inc.); and Bruce Wagman, MBA, RN, RAC (Covance, Inc.). *Roy Baranello and Bruce Wagman spoke to the "Global Forum" to provide the following responses.*

Roy Baranello

Bruce Wagman

Q&A What new, expanded, or different topics are included in this year's Regulatory Affairs & Sciences, Quality & GXP Compliance Track that might have been part of a different track or perhaps not even addressed at previous Annual Meetings?

Roy Baranello: The variety and breadth of topics in general exceed what we've seen previously. There is more emphasis on the global environment, and the program is branching out into topics and regions that previously have not had as much visibility. We certainly have significant representation of US, EU, and Japan-related topics, but new topics such as "GCPs in Emerging Regions" and "Global Marketing Authorizations" have been added to the 2011 program.

There is also a new dedicated "Global Regulatory Agencies" track. This not only dedicates time and space in the program for the regulators to talk about what they think is important and want to get across to stakeholders, but it also allows space for industry-led sessions that include regulators' participation as speakers. It provides for an even broader variety of topics and perspectives on current issues.

The "Global Regulatory Agency" track offers the traditional FDA CDER, FDA CBER, and EMA Town Halls. But now, other regulatory agencies such as the Indian DCGI and organizations such as the network of the European Heads of Medicines Agencies (HMA) also have Town Halls on this year's program. In addition, there is a regulators' session on harmonization of clinical trial requirements in Latin America, and an Asia-Pacific Economic Cooperation (APEC) forum.

That illustrates the change from my perspective: The program includes not only the major regulatory agencies from the countries and regions that have traditionally been represented, but has reached another level in terms of the global scope and representation of different agencies and regions around the world.

Bruce Wagman: The big change for this year is the level of systems integration, quality systems management, and quality risk management that we're identifying in a lot of these sessions. We've gone from a reactive track – in years past, it was always, "How does one react to the regulators?" – to a very proactive stance, where a lot of sessions are going to cover the proactive nature of quality risk management: How we can use a proactive evaluation of the risks associated with key clinical trials and protocols, look at these key risk indicators, proactively evaluate them during the course of the trial, and come up with a better product at the end. We're reducing risk through more upfront, proactive evaluation. This is going to be identified in a lot of the presentations that will be delivered in Chicago.

Q&A In your opinion, how do these changes reflect new and changing industry and regulatory dynamics in 2011?

RB: The changes reflect the global nature of product development and our regulatory environment, and the increasing interest and involvement in parts of the world that perhaps weren't as prominently represented in clinical trials, or even marketing authorizations, until recently. China, India, Latin America, Asia, and other regions have more time devoted to them on the program agenda. And appropriately so, because this mirrors what's actually going on in the world: More clinical trials are being conducted in these countries, and there is growing emphasis on registering products in the emerging markets.

BW: Right now, regulatory authorities are looking at quality management systems instead of just looking at the data that comes out at the end. The expectations

of our regulators are that we'll set up quality management systems that interlink directly between the contract resource organization, various vendors, and the applicant submitting the marketing application. You're going to see that integration in this track this year. You'll see a very strong theme running through our presentations about a systems approach, and then how to evaluate protocols as well as clinical trials in general – a portfolio of clinical trials – to understand their risks and proactively ensure that these problems don't occur.

Q&A You have provided leadership to this track for several Annual Meetings. In what other ways has this track grown and changed during this time?

RB: The program offers different types of sessions now; not just the traditional sessions but also forums and workshops, and I think these changes will stimulate interest by adding more variety with respect to how these topics are presented.

At the same time, many of the most important and current topics are still represented in the track. Global pediatrics development, for example, has been part of the program for a number of years. But it continues to be important, so we have sessions on that topic in the 2011 program. Orphan product development continues to be very important; there seem to be more and more companies interested in opportunities to develop products for orphan or rare diseases, so it's appropriate that this topic is represented as well. Other examples of important topics covered within the track include GCPs in emerging regions, development of biologics, and biosimilars.

BW: I've attended every DIA Annual Meeting since 1990. I delivered my first presentation, as a poster presenter, for DIA in 1994, and have presented at every Annual Meeting since then. It's very exciting to be part of a DIA Annual Meeting. I've been actively involved with DIA in many facets and this is just one of the most exciting ways to participate.

I've been impressed with the way that Dr. Janet Woodcock and others at the FDA, the EMA, and other regulatory authorities all around the world, have supported DIA Annual Meeting functions. They're outside the standard podium politics and can provide clear examples of things that participants can use in their work life. That's probably been one of the most rewarding parts of this whole experience: We have the ability to bring to the forefront key issues that regulators are thinking about and industry needs to know. ■

Different Formats for Different Learners

Because different people learn in different ways, DIA 2011 will present educational programming in various educational formats. So you can consider your Annual Meeting opportunities before you even arrive in Chicago, each different format is described below.

Forum: A 90-minute blended presentation and panel discussion.

Preconference Tutorial: A half-day or full-day of intensive classroom-style instruction in a specific discipline or subject area.

Session: A 90-minute presentation delivered lecture-style from the podium.

Symposium: A blend of three different 20-minute presentations.

Workshop: A 90-minute conceptual presentation delivered in an interactive simulation or role-playing format.

Spanning the Globe: New Global Agency Track for DIA 2011

DIA 2011 will present the first Annual Meeting track specifically devoted to representatives of regulatory agencies and related organizations from around the world (see sidebar). Although updates from, and interactive Q&A sessions with, regulatory agency representatives have always been important components of every DIA Annual Meeting program, this year is the first Annual Meeting where these sessions are consolidated into their own specific track.

DIA Executive Director Paul Pomerantz shared his reflections about how this new **Global Agency Track** marks another important step down the path toward our association's vision: To serve as a **global forum** for knowledge exchange that fosters innovation to raise the level of health and well - being worldwide.

Q&A Why was this global agency track created for DIA 2011 and what benefits will it provide to meeting attendees?

This new track recognizes that every organization, even governments, now needs global strategies for product and supply chain issues. Companies need them because they need to work within a particular regulatory pathway for a particular product: Are there harmonized standards or are there not? Are there different frameworks for pharmaceuticals than for medical devices? Companies need to consider the strategy of producing their products within certain regulatory considerations.

We are in a truly global industry. Every country is concerned about how drugs get into their country, how testing and research are done, and how quality is ensured throughout the supply chain. I have read that when you take a pill, almost 80% of what goes into it comes from another country. Much of the research and data behind it has also been generated in other countries. Whether you're a patient, a company, or a government, you're thinking of a global framework for getting that product manufactured, getting it to market, and then tracking the safety of that product.

So that's, "Why global?" But the other question is, "Why now?" I would probably throw that back and ask, "Why not before?" When you go to the major DIA meetings – our annual EuroMeeting, this Annual Meeting, our annual Clinical Forum in Europe, our annual meetings in China and Japan and India and elsewhere – the conversations are all about "super-regions" and global topics. This conversation is taking place everywhere and is an important dimension of all these meetings. DIA has certainly benefitted from the long history and credibility that we've built through the International Conference on Harmonization (ICH) and other, related organizations, but now we're thinking on the next level and expanding into non-ICH regions, too. We really need to consider the whole world.

There's a third dimension to this, too. We're all concerned about the quality and safety of these products, but we also need to be concerned about the health of the world. We must be increasingly concerned when we learn about conditions elsewhere because problems in other parts of the world are now problems that we all share. We have sort of a collective responsibility to understand the burden of disease and discover solutions.

This is something that industry is really beginning to embrace. I was just with our Annual Meeting program team as we were speaking to the Gates Foundation about building an Annual Meeting session that shares what the Foundation looks at to facilitate their philanthropic partnerships. There's currently an incredible amount published in numerous journals about how major

pharma is partnering to address the burden of neglected diseases, to come up with vaccines, treatments, and solutions, for diseases in which not much has been invested before. Part of this is just simply recognizing that we have a responsibility. But part of it is also enlightened self-interest. These regions are where the growth is going to be, and we want to make sure that DIA helps you provide health care products and services in these regions, because that's going to be your future. We're all on one very tight planet now. Looking at the global regulatory framework is an important part of all of us working together.

DIA is unusual because we provide the only place – the only meeting in the world – that regulators feel is "the place to go." I've been to a lot of meetings, as you can imagine, and I've never seen this anyplace else. You'll see regulators from a specific nation, or a group of nations or even regions, but you won't see them all, from every place. It's a unique role that DIA is fortunate to play. Regulators within emerging countries, in particular, really look at the DIA Annual Meeting as an important place to come.

It's also interesting to note that there aren't really any "global regulators" at all, but regulators from different countries and regions who work in a shared global environment.

Paul Pomerantz

Q&A What benefits will this consolidated, global track provide to regulators and other speakers within it?

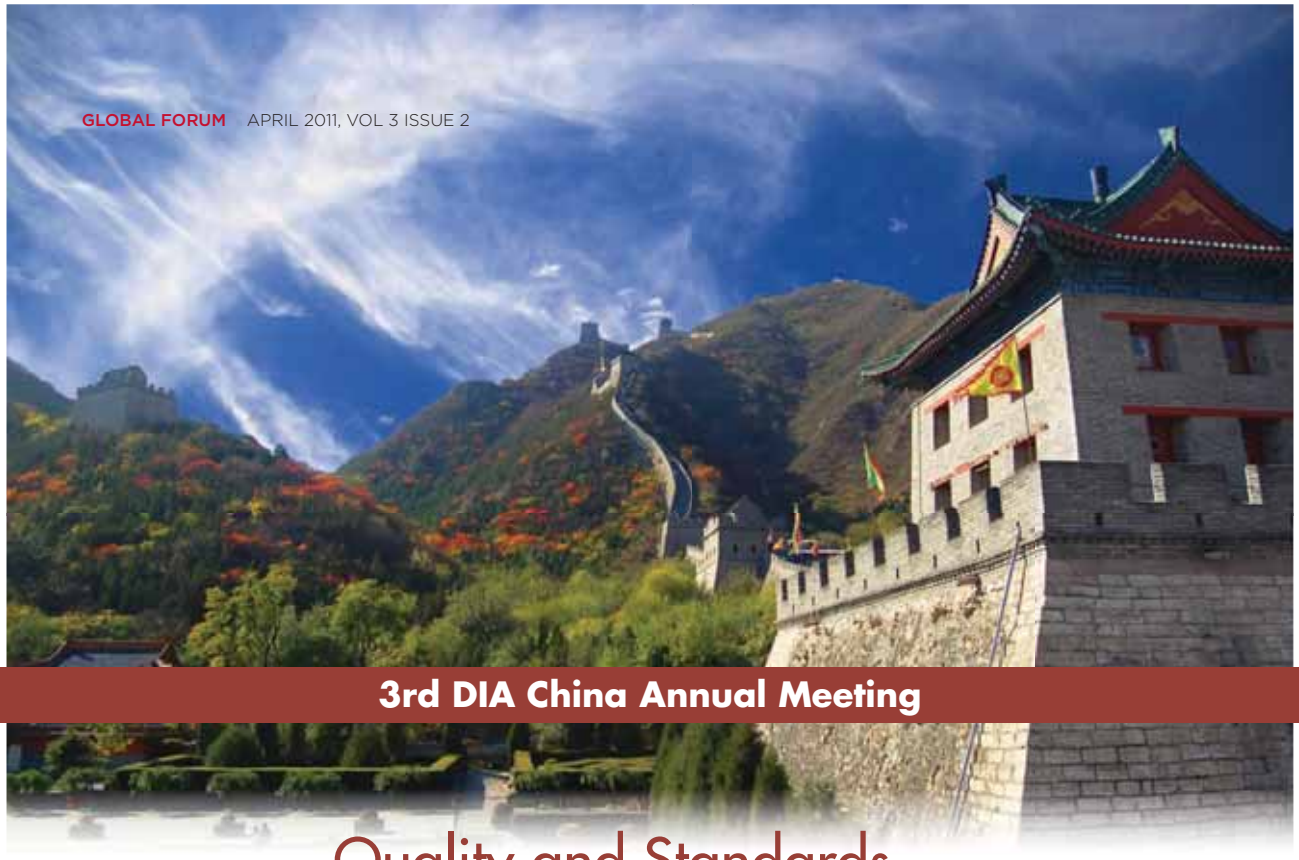
While development of this track fully recognizes that each framework is different, the benefit of this track to the regulators is that they'll be able to learn together and from each other: What are their similar, and different, experiences? What are their problems? How are you solving this problem or how can we get together to solve this problem?

There's a real hunger among regulators to build a global network. DIA is looking at a couple different means to do this. The global regulatory perspectives consolidated into our annual EuroMeeting and European Clinical Forum, this DIA 2011, and similar events, are very important places from which to start. But we're also implementing, as part of our strategic plan, what we're currently calling a Global Regulatory Agency Forum which, while still in development, we envision will be a venue where regulators can share with DIA their major priorities and concerns – what keeps them up at night – so that DIA can help. We don't often have those kinds of conversations, and they're very eager to begin.

We're also looking to tie in the DIA ConneX component of the Digital Initiative, another large part of our strategic plan, to create a DIA ConneX forum for global regulators to identify problems and share whitepapers and other documents. There's nothing like this in the world. As a nonprofit and neutral global association, DIA can provide a safe place for these challenging discussions. In turn, they'll give our DIA Board, our SIACs, and our volunteer committees a better sense of what we can do to help. ■

The following regulatory and related agencies and associations have confirmed that their representatives will speak, or host their own sessions, at DIA 2011:

- Agency for Healthcare Research & Quality (AHRQ)
- Italian Medicines Agency (AIFA)
- Federal Institute for Drugs & Medical Devices, Germany (BfArM)
- Center for Drug Evaluation, Taiwan
- Centers for Drug Evaluation & Research (CDER) and Biologics Evaluation & Research (CBER), US FDA
- Federal Commission for the Protection against Sanitary Risk (COFEPRIS), Mexico
- Central Drugs Standard Control Organisation of India & FDA Gujarat, India
- European Directorate for the Quality of Medicines & Healthcare (EDQM), EU
- European Heads of Medicines Agencies (HMA), EU
- European Medicines Agency (EMA), EU
- Health Canada, Canada
- Institute De Salud Publica De Chile (ISPCH)
- Korean Food & Drug Administration (KFDA)
- Medicines Evaluation Board, The Netherlands (MEB)
- Medicines & Healthcare Products Regulatory Agency (MHRA), UK
- Medsafe, New Zealand Medicines & Medical Devices Safety Authority
- National Cancer Institute (NCI)
- National Institutes of Health (NIH)
- Pharmaceuticals and Medical Devices Agency (PMDA), Japan
- Therapeutic Goods Administration (TGA), Australia



3rd DIA China Annual Meeting

Quality and Standards — Elevating China Pharmaceutical Development

The 3rd DIA China Annual Meeting will be held from May 15 – 18, 2011 at the Crowne Plaza Sun Palace, Beijing. The Annual Meeting is again jointly hosted with the China Center for Pharmaceutical International Exchange (CCPIE) of the State Food and Drug Administration (SFDA). The theme of the meeting is "Quality and Standards — Elevating China Pharmaceutical Development."

This 3rd DIA China Annual Meeting will serve as an international and neutral forum to discuss and explore the latest developments within the pharmaceutical industry in China, as well as the ideas that will impact global health. The program is co-chaired by James CAI, MD, President, Pangu Biopharma Ltd., member of the DIA Advisory Council of China, and ZHAO Yajun, Director-General, China Center for Pharmaceutical International Exchange, SFDA. The Vice-Chairperson is John J. HU, PhD, Vice President, International General Manager, USP-China and also a member of the DIA Advisory Council of China.

The conference will feature a opening plenary session on May 16 with a high-level keynote speaker, as well as a unique open debate by senior professional, top academics and high-level officials from pharma, R&D, and regulatory agencies.

This multitrack three-day conference features key speakers from China and other countries, covering topics including:

- CMC/cGMP
- Clinical Research and Drug Safety
- Regulation and Implementation
- Clinical Data Management and Statistics
- Medical and Scientific Affairs
- Capability and Capacity Building for Clinical Development
- QA/QC in Clinical Development

The Annual Meeting includes an Exhibition and a Student Poster Session during the main conference and will be preceded by several preconference workshops on May 15. All events will take place in the Crowne Plaza Sun Palace in Beijing.

For further information please contact DIA China at +86 10 5923 1109 or dia@diachina.org. The submission deadline for the Student Poster call is April 10, 2011. For poster submissions, exhibits and advertisement opportunities please contact Ms. Runshan CHEN at ting.chen@diachina.org. ■

1ST DIA CLINICAL PROJECT MANAGEMENT TRAINING COURSE HELD IN CHINA

Clinical trials have become more complex, and there is a great need in China for knowledge exchange and skill training to effectively design and manage clinical studies. To help meet this need, DIA successfully held the first Clinical Project Management Training offered in China on February 24-26 at the Beijing Jade Palace Hotel in Beijing. With over 70 participants, the intensive three-day course provided systematic and in-depth training in the fundamentals of clinical project management. Participants included physicians, study managers, and clinical research associates representing multinational and local companies, CROs, hospitals, and universities.

Cris M. Howard facilitates discussion after an interactive group assignment.

The program was chaired by QingAn JIAO, Head of Clinical Operations, Asia Pacific, Roche Product Development in Asia Pacific. The lead instructor, Cris M. Howard, Senior Clinical Project Manager, Emergent BioSolutions, has a wealth of experience in teaching Clinical Project Management for DIA globally. To customize the program to address the challenges unique to China, Cris collaborated with Ning XU, Executive Director of Clinical Development Services, Covance China, and Paul DAI, Director, Regional Head of ICRO, AMAC/Greater China, Novartis. All of these instructors have been active DIA volunteers for many years.

The Clinical Project Management Training is a key course within the DIA training curriculum. The three-day course covers 12 modules, including understanding the value of clinical project management, producing a project schedule, estimating enrollment, determining a staffing plan, leading teams, managing risk, forecasting a budget, executing the plan, and managing project scope. The highly interactive set-up of the program includes case assignments, small group discussions, and unique close interactions between participants and instructors.

Program Chair QingAn Jiao was very pleased with the success of the training: "Participants liked the course very much, and valued the presentations, interactions, and case studies." Cris M. Howard added that "It is a great honor and privilege to give back to this uniquely complex biopharmaceutical industry that has given us so much. Together, we can forge a path to enable success for those who follow in our footsteps." ■

www.diahome.org

UPCOMING EVENTS

In the Americas
Conferences

MAY 3-4, 2011
Dried Blood Spot Sampling in the Pharmaceutical Industry: Three Years of Experience and Implementation
Philadelphia, PA

MAY 4-5, 2011
DIA/FDLI The Future of Biosimilars in the US: Legal, Scientific, Regulatory, Clinical and Payer Issues
Bethesda, MD
Co-sponsored with Food & Drug Law Institute (FDLI)

MAY 12-13, 2011
FDA Information Day: The New Individual Case Safety Report (ICSR) International Standard and ICH E2B
Alexandria, VA

MAY 13, 2011
Best Practices for the Prevention of Cargo and Warehouse Theft of FDA Regulated Medical Products and Infant Formula
Rockville, MD

JUNE 19-23, 2011
DIA 47th Annual Meeting
Chicago, IL

In the Americas
Training Courses

JUNE 17-19, 2011
Regulatory Affairs Part I: The IND Phase
Chicago, IL

JUNE 17-19, 2011
Fundamentals of Clinical Research Monitoring
Chicago, IL

JUNE 17-19, 2011
Clinical Project Management
Chicago, IL

JUNE 17-19, 2011
Introduction to Good Clinical Practices and Auditing
Chicago, IL

JUNE 18-19, 2011
Risk Management and Safety Communication Strategies
Chicago, IL

JUNE 18-19, 2011
New Drug Product Development and Lifecycle Management
Chicago, IL

JUNE 19, 2011
Art of Writing a Clinical Overview
Chicago, IL

Europe
Conferences

MAY 10-12, 2011
5th European Forum for Qualified Person for Pharmacovigilance (QPPV)
London, UK

MAY 23-24, 2011
Clinical Trial Registries
Basel, SWITZERLAND

MAY 26, 2011
Influence of the EU Legislation on the Bulgarian Drug Industry - A Workshop organised by the DIA Advisory Council of Europe
Sofia, BULGARIA

JUNE 6-7, 2011
European Regulatory Affairs Forum
London, UK

JUNE 8, 2011
Product Information Forum
London, UK

Europe
Training Courses

MAY 04-06, 2011
Authorisation of Biopharmaceuticals, Biosimilars and Advanced Therapies in Europe
Basel, SWITZERLAND

MAY 9-10, 2011
Introduction to Signal Detection and Data Mining
Pharmacovigilance
Amsterdam, THE NETHERLANDS

MAY 9-13, 2011
Non-Clinical Safety Sciences and Their Regulatory Aspects
Leiden, THE NETHERLANDS

MAY 10, 2011
EudraVigilance Information Day at the European Medicines Agency
London, UK

MAY 10-11, 2011
How to Prepare for Pharmacovigilance Audits and Inspections
Amsterdam, THE NETHERLANDS

MAY 16-17, 2011
Building the eCTD – Practical Solutions to Compile Electronic Submissions
Nice, FRANCE

MAY 16-18, 2011
Practical Guide for Pharmacovigilance: Clinical Trials and Post-Marketing
Nice, FRANCE

MAY 18-20, 2011
Essentials of Clinical Study Management
Prague, CZECH REPUBLIC

MAY 19-20, 2011
Benefit/Risk Management
Prague, CZECH REPUBLIC

MAY 30-31, 2011
European Regulatory Affairs: In-depth Review of Current Registration Procedures in the European Union
Basel, SWITZERLAND

JUNE 6-9, 2011
Good Management of Medical Devices and In-vitro Diagnostics
Basel, SWITZERLAND

JUNE 7, 2011
Introduction to Pharmacovigilance and Electronic Transmission of Individual Case

Safety Reports (ICSR) for the use of Eudravigilance
London, UK

Japan

Conferences

MAY 10-11, 2011
5th Annual Conference in Japan for Asian New Drug Development
Tokyo, JAPAN

JUNE 1-2, 2011
2nd Cardiac Safety Workshop in Japan
Tokyo, JAPAN

Starting in JUNE, 2011
4th Regulatory Affairs Training Course in Japan
Tokyo, JAPAN

OCTOBER 27-28, 2011
8th DIA Japan Annual Meeting
Tokyo, JAPAN

In Other Regions

Conferences

APRIL 26-28, 2011
Asia Regulatory Conference
Seoul, KOREA

MAY 16-18, 2011
3rd DIA China Annual Meeting: Quality & Standards: Elevating China Pharmaceutical Development
Beijing, CHINA

Webinars

APRIL 29, 2011
1:00 – 2:30 PM ET
CDER Town Hall: FDA Discusses Latest eCTD Updates

MAY 4, 2011
11:00 -12:30 PM ET
2011 Guidance for Industry Process Validation: General Principles and Practices

MAY 17, 2011
11:00 -12:30 PM ET
FDA Discusses Final Rule to Reclassify Medical Device Data Systems (MDDSs)

Monitor www.diahome.org for upcoming webinars as they become available and archived webinars that have already taken place.

eLearning

Medical Communications eLearning Certificate Program

Clinical Investigator eLearning Program

Informed Consent Module

Kaplan EDuNeering

Clinical Pharmaceutical eLearning Program
Clinical Medical Device eLearning Program
GMP Pharmaceutical eLearning Program
Validation and Part 11 Compliance eLearning Program

Basics of the PhRMA Code
Basics of the AdvaMed Code
Eucomed Guidelines on Interactions with Healthcare Professionals
Foreign Corrupt Practices Act
Introduction to Medical Device Compliance
Global Anti-bribery

Zenosis by Intellego

Variations to Marketing Authorisations in Europe
Registration of Monoclonal Antibodies
The ANDA: Requirements for Obtaining FDA Approval for Generic Product in the US
Pharmacokinetics and Pharmacodynamics (PK/PD) in Drug Registration

Online Training Series

MAY 2 - 13, 2011
12:00PM – 1:00PM
Basics of the IND

MAY 3 – 24, 2011
12:00PM – 2:00PM
Good Clinical Practices for the Clinical Research Professional

MAY 5 and 6, 2011
12:00PM – 1:30PM
Developing Standard Operating Procedures (SOPs)

MAY 9 -18, 2011
11:30AM – 1:00PM
Introduction to Computer Systems Validation

MAY 16 – 26, 2011
12:00PM – 1:15PM
Basics of the NDA

JUNE 1 and 2, 2011
12:00PM – 1:00PM
Interactions with the FDA during the IND/NDA Phases

JUNE 9, 2011
12:00PM – 1:30PM
Regulatory Aspects of Prescription Drug/Biologics Advertising and Promotional Labeling
Online Training Course

EudraVigilance

Electronic Reporting of ICSRs in the EEA

MAY 2-4, 2011 – Paris, FRANCE
MAY 18-20, 2011
MAY 23-25, 2011
JUNE 8-10, 2011
JUNE 20-22, 2011

EudraVigilance Information Day (10th)

MAY 10, 2011

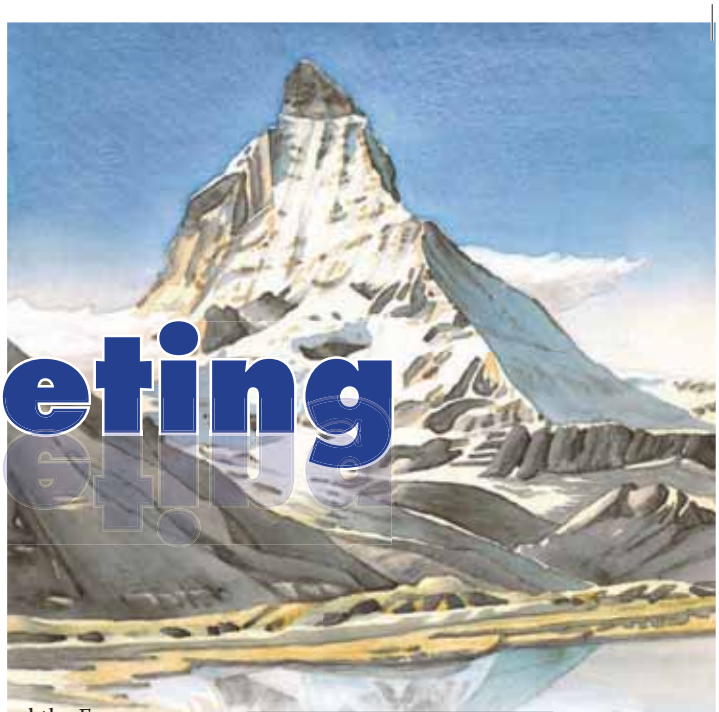
Medicinal Product Dictionary (EVMPD)

MAY 5-6, 2011 – Paris, FRANCE
MAY 26-27, 2011
JUNE 23-24, 2011

Introductory Course

JUNE 07, 2011

Award Winners at the EuroMeeting



The DIA Awards Ceremony at the 23rd Annual EuroMeeting took place during the plenary session on Monday, 28 March 2011 in Rooms A+B+C of the Palexpo in Geneva, Switzerland.

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

Distinguished Career Award Martin Terberger

Following studies in veterinary medicine and a year in veterinary practice, Dr. Terberger joined the Public Veterinary Service of Lower Saxony, Germany, in 1989. Between 1990 and 1995, he worked for the German Federal Ministry of Agriculture as an expert on international trade.

Martin Terberger

Dr. Terberger joined the European Commission in 1995. During his 15 years at the European Commission, he served in a number of roles, including veterinary expert, Assistant to the Director-General for Health and Consumer Affairs, and Head of Unit positions dealing with planning, relations with the other institutions, personnel matters, and budgetary concerns. He was Head of the Pharmaceuticals Unit of Directorate-General Enterprise from 2005 – 2010.

Dr. Terberger has been a regular speaker at DIA meetings over the years and has made an important contribution towards developing the relationship between DIA and the European Commission.

Founders' Service Award Sabine Brosch

Sabine Brosch is Business Lead for EudraVigilance and International Standardisation in Pharmacovigilance at the Pharmacovigilance and Risk Management Sector of the European Medicines Agency (EMA). She obtained a Masters Degree in pharmacy and a Doctor of Natural Sciences Degree in pharmacology from the University of Vienna. She also performed postgraduate studies in pharmacology at the University of Melbourne and Auckland.

Sabine Brosch

Mrs. Brosch joined the EMA in 1996. Prior to this, she worked as an assistant professor at the Department of Pharmacology and Toxicology at the University of Vienna and at the Pharmacovigilance Department at the Austrian Ministry of Health.

Mrs. Brosch is the EMA representative of DIA's European Training Sub-Committee and has been working with DIA to develop and provide training programs since 2004. She further developed a Memorandum of Understanding (MoU) to define DIA's role in acting as a conference organizer for the EMA in the area of EudraVigilance and pharmacovigilance up to 2014. She took a leading role in preparing large-scale training programs in the area of electronic

reporting of Individual Case Safety Reports (ICSRs) and EudraVigilance. Furthermore, she developed a dedicated "Excellence in Pharmacovigilance" training program with a team of experts from the EMA, the pharmaceutical industry, and DIA. The tenth such course took place at the Agency's premises in February 2011. In addition, she is a member of the program committee responsible for organizing dedicated Information Days related to EudraVigilance and international standardization projects in pharmacovigilance along with experts from the US Food and Drug Administration (FDA).

Outstanding Service Award Pierre-Yves Lastic

Dr. Pierre-Yves Lastic studied biology, computer sciences, and languages in France and Germany. He holds a PhD in biology from Bayreuth University, Germany. After years of research and teaching at Bayreuth University, he joined the pharmaceutical industry, where he spent 20 years in different management positions in the field of clinical research.

Pierre-Yves Lastic

He is currently an expert on standards for health information exchange and is the Senior Director, Data Privacy & Healthcare Interoperability Standards, at sanofi-aventis, France.

Dr. Lastic is a board member of the International Pharmaceutical Privacy Consortium and Chairman of the IPPC European Group, as well as a board member of the Clinical Data Interchange Standards Consortium and Chairman of CDISC Europe.

Pierre-Yves has served DIA in a number of volunteer positions. He is a member of the Advisory Council for Europe (ACE) and has been a member of the program committee, session chair, session speaker, and tutorial instructor for numerous DIA meetings.

Outstanding Service Award Gesine Bejeuhr

Dr. Gesine Bejeuhr started her c areer as an inspector (for pharmacies, hospitals, GMP) and scientific administrator with Health Authorities in Germany (one-year-secondment to European Medicines Agency's inspections sector).

Gesine Bejeuhr

Prior to joining the Research-Based Pharmaceutical Companies Association (vfa) she was responsible for Regulatory Affairs & Safety Intelligence at Grunenthal, Germany. She dealt with the cross-functional implementation of new legislative requirements such as the EU Paediatric Regulation and participated in EFPIA's Regulatory Affairs group. She currently is the Senior Manager Regulatory Affairs/Quality, vfa Research-Based Pharmaceutical Companies, Germany.

Gesine has been actively involved with DIA for several years as speaker, session chair, and program committee member for various workshops and conferences including EuroMeetings and DIA Annual Meetings. She is a Theme leader for the EuroMeeting 2012.

Gesine is also a member of the DIA Advisory Council of Europe (ACE). She was one of the initiators of a series of complimentary ACE workshops in Central and Eastern Europe. At present, Gesine is chair of the DIA Pediatric Special Interest Area Community (SIAC), consisting of European and US experts. In this capacity, she organizes monthly SIAC calls. The SIAC also prepares sessions for both the EuroMeeting and Annual Meeting and runs specific pediatric conferences.

As an industry representative and association member, Gesine continuously strives to strengthen the dialogue between all stakeholders involved in the health system. ■

WATCH OUT FOR THE NEW AND COLORFUL REGULATORY AFFAIRS LANDSCAPE

DIA will present its 2011 Regulatory Affairs Forum on 6-7 June at the Hotel Novotel London West, in London, UK. The meeting will focus on the new and colorful regulatory affairs landscape – how to integrate pharmacovigilance and health technology into regulatory strategies that are becoming more transparent. This very interesting gathering of high-level European specialists involved in the in the field of regulatory affairs has been scheduled to allow participants cost-effective travel with just one overnight stay. It is followed by a one-day workshop on product information on 8 June 2011.

Programme Co-Chairs

Gesine Bejeuhr, Reg. Aff./Quality, vfa-Researched-Based Pharm. Comp., Germany

Brenton James, Strategic Consultant Strategic Regulatory Affairs in the EU, UK

Programme Committee

Peter Arlett, Head of Pharmacovigilance and Risk Management, EMA, EU

Peter Bachmann, European Drug and International Affairs, BfArM, Germany

Tony Humphreys, Head of Regulatory, Procedural and Committee Support, EMA, EU

Trine Moulvad, VP, Reg. Aff., Diabetes+Obesity Projects, Novo Nordisk A/S, Denmark

Alban Dhanani, Head of the Registration Procedures and European Affairs Unit, Afssaps, France

Programme Co-chairs Gesine Bejeuhr and Brenton James disscussed the upcoming conference for *Global Forum* readers.

Regulatory affairs will be greatly affected by the changes implied in the pharmacovigilance part of the so-called Pharma package. The legislation was published early this year, and the ball is now in the field of those who will work with these new regulations in the future. Regulatory professionals will have to adapt to these changed options and regulators are keen to apply their new tools, but how does this work together? Peter Arlett chairs the opening session, and he and the speakers in his session might shed some light on this question.

The key measures and impacts of the new pharmacovigilance legislation will be presented and put into the context of ongoing EU strategies to strengthen the life-cycle benefit-risk monitoring of medicines. This will focus on the need for strong legislation, robust science, closer collaboration between Regulatory and Pharmacovigilance functions and sufficient resources.

Agencies are challenged by the need to meet public demands for greater transparency and openness with respect to their activities, their decision-making processes, and the ready availability of up-to-date information on medicinal products, adverse drug reactions, and clinical trials. Both EMA and the Heads of Medicines Agencies (HMA) have included strategies how to meet these demands in the future. Truus Janse de Hoog and her speakers will explain how the implementation of these measures will also ensure industry's interest to keep the commercially confidential details out of the published documents.

Two very experienced chairs (Brenton James and Tony Humphreys) are working on the session that covers the changing environment of the CHMP and the Centralised Procedure. They will make sure that participants get pieces of information that are new to them even if they have been working in regulatory affairs for years. And in an informal setting, participants will have the chance to discuss their "burning" questions with key EMA decision makers.

The National Competent Authorities' (NCA) most important regulatory committee, the Coordination Group for Human Medicinal Products (CMDh) is also challenged by the new regulatory environment with new responsibilities. The European Commission issued a survey on some ideas about how to shape the landscape for clinical trials in Europe. Whereas initially a centralized procedure for clinical trial authorizations was discussed, the Voluntary Harmonisation Procedure was introduced by the HMA to show the efficiency of the NCA network. Peter Bachmann will convene speakers to discuss these topics on the second day.

An increasing number of medicinal products are combined with medical devices. In the past it was mainly application devices, but now there is a new group, "companion diagnostics" as well as medical devices to be used together with molecular imaging agents. Is the medicinal legislation still appropriate to meet the needs for these new products?

The growing importance of health technology assessment (HTA) bodies on the access to market of novel medicines will be addressed by Karl Broich and Gesine Bejeuhr in the last session of this conference. It will be put in perspective with the work that the regulatory agencies do when they assess medicinal products. The relative effectiveness of pharmaceuticals will be studied in future and is one part of the HTA decisions. However, the regulatory agencies will have their scientific say first.

Early-Bird Savings

Register by 25 April to receive the Early-Bird discount and save EUR200. Reference Event #11108. We hope to see you there. ■

PRODUCT INFORMATION FORUM 2011

This year's Product Information Forum will take place on 8 June 2011 at the Hotel Novotel London West, in London, UK.

Many stakeholders have recently raised concerns about the usefulness of the current static Product Information, which has been nearly unchanged for several years. The critics are numerous, and nobody seems to be happy with the currently existing content and format, which are regulated by EU-wide legislation and part of the marketing authorization of any medicine licensed in Europe.

Angelika Joos, Head Regulatory Policy, EU & Most of World, Merck Sharp and Dohme (Europe) Inc., Belgium, serves a programme co-chair for the Product Information Forum. She provided the following commentary on this upcoming conference for the *Global Forum.*

During the recent parliamentary debate of the so-called "pharma package," this topic has once again been fiercely debated, but due to time constraints it could not fully be addressed in the ongoing process. As a result, the new Pharmacovigilance Legislation which was published in the Official Journal on December 31, 2010, is now tasking the European Commission to provide a report on the current product information and its usefulness to stakeholders by January 2013. This report shall be presented to the European Parliament and the Council and "assess the current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals. The Commission shall, if appropriate, and on the basis of the report, and consultation with appropriate stakeholders, present proposals in order to improve readability, layout and content of these documents."

DIA is organizing this Product Information Forum with the aim of trying to identify challenges and opportunities for developing a new vision for agency-regulated medicine information that may better meet various stakeholder needs and take into account the future developing space of eHealth.

The Program Committee has invited speakers from patient organizations,

health care providers, academia, regulatory agencies, and industry to present and debate their current thinking. The speakers will discuss the current situation from their various perspectives. So what is actually wrong with the current information and how can we develop new ideas for a future vision?

Industry will explain the complexities of the global labeling development process within large pharmaceutical companies. Gaining a better understanding around product liability issues that are tied to the provided product information and are setting the legal boundaries is another key goal. Learnings and experience from ongoing national initiatives in Sweden, Germany, and the UK that may be useful for a broader European approach will be presented and discussed. Those initiatives involved very fruitful interactions between patients, industry, and regulators to develop models for better addressing the end-users needs.

But the communication world is changing rapidly, and the provision of information and education to stakeholders in today's Internet world may offer significant new opportunities to enhance compliance and understanding by using new communication technologies and social media versus the traditional printed leaflets provided in the medicines pack. To further enhance the important messages to the users, the use of smart design and pictograms may also provide additional value to this important medical communication tool.

We expect that this conference will provide an interesting debate and spark new ideas for moving this field forward. ■

Program Chairs

Angelika Joos, MPharm
Head, Regulatory Policy, EU and Most of World
Merck Sharp & Dohme Inc., Belgium

Fiona Reekie
Director, Global Regulatory Policy & Intelligence EMEA
Janssen Pharmaceutical Companies of Johnson & Johnson,
United Kingdom

Program Committee

Jan MacDonald
Head, Patient Information Quality
MHRA, United Kingdom

Elisabeth Fournier-Qezari
Director Regulatory Intelligence EU & Other Regions
Sanofi Aventis, France

Merete Schmiegelow, MPharm,MSc
Director, Regulatory Policy & Intelligence
Novo Nordisk A/S, Denmark

Online registration is available or contact Michael Hediger (Michael.Hediger@diaeurope.org; +41 61 225 51 51)

1st DIA India Cardiac Safety Conference

J. Rick Turner

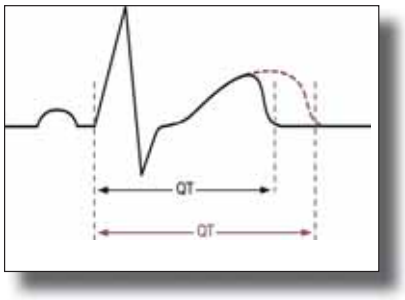
The 1st DIA India Cardiac Safety Conference took place on March 12 at the Hotel Westin in Mumbai. Program Chair Dr. Snehal Kothari and Program Committee Members Drs. Dhiraj Narula and Rick Turner assembled a program that addressed issues of importance to a wide range of professionals in drug development, including clinicians, clinical trialists, and operational experts.

There is increasing interest in drug safety and patient safety among multiple stakeholders, including government agencies, regulatory agencies, pharmaceutical and biopharmaceutical companies, patient advocacy groups, the media, and, not least, prescribing physicians and their patients. The cardiac and cardiovascular safety of drugs has been placed at the forefront of drug safety initiatives by two ICH guidelines, ICH S7B and ICH E14 (both released in 2005, with associated "Questions & Answers" documents being released more recently for ICH E14), and by FDA and EMA guidance concerning the development of antidiabetic drugs for type 2 diabetes mellitus (T2DM) released in the last couple of years. Cardiovascular safety assessments, and the prospective exclusion of unacceptable cardiovascular risks, are therefore very important considerations for biopharmaceutical sponsors.

ICH guidelines S7B and E14 address the propensity of a drug to induce a particular polymorphic ventricular arrhythmia, *Torsades de Pointes*, which is rare and often self-correcting, but also potentially fatal. Attention focused on such proarrhythmic liability following the high-profile withdrawal from the market of drugs such as terfenadine (an antihistamine) in the 1990s. While proarrhythmic liability is still a central and important focus of regulatory concern, and was a central component of this conference, the field of integrated cardiovascular safety has become much broader. Particularly noteworthy are the high-profile cases of rofecoxib (voluntarily withdrawn from the worldwide market by its sponsor in September 2004) and rosiglitazone (still on the US market with an associated Risk Evaluation and Mitigation Strategy [REMS]).

The conference opened with welcoming comments from Sultan Ghani, Director, DIA India. Additionally, he put the content of the meeting and pharmaceutical drug development into a global context. Dr. Lokhandwala gave the first talk, introducing the topic of drug-induced QT prolongation and its assessment. The QT interval as seen on the surface electrocardiogram (ECG) represents the length in the time domain between the onset of the QRS complex and the offset of the T-wave. Figure 1 provides a stylistic representation of the QT interval, and also QT interval prolongation. QT interval prolongation represents delayed repolarization of the cardiac muscle cells.

Figure 1



The inherited condition of Long QT Syndrome (LQTS) comprises a

a family of abnormal genetic variants that lead to a prolongation of the QT interval, a condition of considerable clinical concern since it is associated with syncope and *Torsades de Pointes*. Acquired QT prolongation, including drug-induced prolongation, is also of considerable clinical concern since, while the mechanism is different, the resulting clinical phenomenon can be the same. ICH E14 describes a specialized preapproval clinical trial, the Thorough QT/QTc (TQT) Study, designed to look for drug-induced QT prolongation liability in a particularly rigorous manner. Different talks throughout the conference focused on various aspects of this study, including: the digital ECG technology needed; the timing of the study in earlier phases of a preapproval clinical development program; the collection, analysis, quality control, and regulatory submission of ECG waveforms and measurements; and the assessment of ECG parameters in later phase preapproval clinical development.

Widening the discussions to a broader range of cardiovascular considerations, the final talk by Dr. Turner discussed the assessment of cardiovascular risk for new antidiabetic drugs for T2DM. In this domain, the events of regulatory interest are clinical endpoints. The traditional major adverse cardiovascular events (MACE) composite endpoint is commonly used in such settings, which includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Other adverse advents, such as acute coronary syndrome and urgent revascularization procedures, can also be included. A composite endpoint can be usefully employed since the number of individual events may be too low to meaningfully compare those occurring in the test drug treatment group with those in the comparator treatment group. As in the TQT study, a three-component model, comprising clinical, regulatory, and statistical science, is employed to prospectively identify unacceptable cardiovascular risk. The conference was then brought to a close by Program Chair Dr. Snehal Kothari.

Drs. Snehal Kothari, Niraj Vyas, Dilip Karnad, Dhiraj Narula, and Rick Turner.

Following a very interesting and enjoyable day, Dr. Kothari expressed his thanks to the attendees for their participation. "An outstanding characteristic of this meeting was the active participation of the attendees, which was very evident from the excellent questions they asked and the comments that they made. The 'Questions & Answers' sessions that followed each presentation were therefore very instructive in themselves." In addition to speakers from Quintiles' core ECG lab in Mumbai, their Medical and Scientific Directors traveled from the United States to take part in the conference. "Following the very successful 1st DIA Japan Cardiac Safety Conference that was held in May 2010," noted Dr. Kothari, "it is very pleasing to see the inaugural DIA India event become a reality, with enthusiastic attendees very keen to learn from, and to share their own experiences with the speakers."

Dr. Deepa Desai, Global Head, Quintiles Cardiac Safety Services, thanked DIA for their support of this meeting, and for the invitation to her team members to speak. "It has been a most interesting day, and the first of what we hope will become a regular series of meetings. As well as members of industry, we would like to have representatives from regulatory agencies and academic medical centers speak at future events to get perspectives from these stakeholders too."

J. Rick Turner, PhD, is Senior Scientific Director, Integrated Cardiovascular Safety, Cardiac Safety Services, Clinical Development Services at Quintiles. Rick is also the editor-in-chief of the *Drug Information Journal.* ■

The Strategic Outsourcing of

CDM, Biostatistics, Programming and Medical Writing Services – Destination India

Nimita Limaye

Clinical data management, biostatistics, programming and medical writing are functions that have been increasingly outsourced to India. With a large pool of highly qualified scientific and medical professionals, strong IT domain expertise, increasing experience in effectively leading FSP engagements, and without having to address regulatory compliance requirements more critical to the conduct of clinical trials, India clearly stands out as a destination of choice for the outsourcing of these activities. Success would depend on the commitment of the industry to invest in growing the talent pool rather than "body swapping," which only results in ever-increasing costs and defeats the very basis of onshoring. Strategic FTE FSP partnerships clearly override individual project outsourcing and are a statement of confidence defining long- term consolidated partnerships.

India has been a key destination for the outsourcing of clinical data management, biostatistics and programming, and medical writing services. Despite the recession and the many concerns about jobs being transferred offshore, "… many companies do not understand that outsourcing isn't about exporting jobs, it's about importing innovation."[1] Transformational outsourcing, not just low costs and good quality, but the value-add that vendors provide through "street smart innovation" is what will truly make the difference today.

A study conducted on over 30 biopharma companies by PRTM demonstrated that the majority of the companies outsource nearly 50 percent of their clinical monitoring and nearly 75 percent of their clinical data management activities when conducting their clinical trials in Asia.[2] A Vendor and Outsourcing Survey conducted by CenterWatch indicated that of 27 companies surveyed, data management (44%) was the second most frequently outsourced activity after clinical monitoring (59%), closely followed by medical writing (41%) in fourth place and statistical analysis (37%) in sixth place.[3] The AT Kearney's Global Services Location Index,™ 2011, indicated that in spite of the shifting macroeconomic environment, India still retains the first position as the destination of choice for outsourcing, followed by China and Malaysia. India's strength clearly lies in its people skills and availability, leading not only in terms of the size and availability of its labor force, but also as the outright leader in terms of resources having relevant experience and language skills. China is strong in terms of providing high-end analytics and advanced IT capabilities, but Indian companies such as TCS, Infosys. and Wipro have already set up their operations in China as well.[4]

Strategic outsourcing for clinical data management, statistical programming, and medical writing by mid to large pharma or biotech companies usually follows the Functional Service Provider or Full Time Equivalent model. While one company may choose to partner with different vendors for each of these services, as consolidation of vendors occurs, sponsors would prefer to partner with a single vendor. Challenges to the sponsor as a result of this model include increased levels of oversight, a loss of resource control, despite retaining project control, and a loss of immediate access as a result of offshoring. However, advantages such as retaining organizational knowledge and trained resources as a result of having a dedicated team, the ability to be able to deal with lean periods as well as with spikes in work volumes related to submission activity without incurring an increase in fixed costs, and minimizing contracting costs by working with preferred partners through Master Services Agreements, do offset the same.[5] These are models which vendors prefer as well as a result of better branding, resulting from being chosen to be the preferred partner to

support a leading pharma company, stable revenue inflows, and lower infrastructure costs (as sponsors usually prefer that the vendor's team works on their applications and processes), among other reasons.

Keys to the success of these models include working with a vendor that has leadership with experience in managing this business model, establishing the right governance models, senior leadership commitment, high levels of transparency on both sides, clarity at the start of the engagement regarding SLAs (Service Level Agreements), having the right issue escalation plans and risk management strategies in place, sharing a long-term vision, and finally investment from both sides in establishing a rapport and celebrating the partnership.[6]

Clinical data management, biostatistics and programming, and medical writing have their own unique features and associated challenges.

The most extensively outsourced service among these three has probably been clinical data management. Growing primarily over the past five years in India, with an increasing number of training institutes offering certificate courses in this domain and a large number of global pharmas and CROs establishing their offshore operations in India, what was once a niche talent pool has now become more readily accessible. However, experience levels in this domain, as in the case of the other two, differ considerably across the west and the east. While services are moving up the value chain in India, the data manager's role needs to become more comprehensive (as against being more specialized, which typically results from many of the FSP models which are established in India), and a better understanding of global regulations and standards is required. A CCDM (Certified Clinical Data Manager) certification from the Society of Clinical Data Management serves as an additional stamp of credibility, and the majority of international CCDMs come from India.[7] In addition, experience is often restricted to a single application such as Oracle Clinical or INFORM and needs to spread across applications as well. What CROs in India leverage well, however, is the clinical edge to data review, as medically qualified professionals serve as a readily available asset in this geography.

Medical writing is still a relatively niche skill in India, and experienced resources are not easy to find. With limited educational opportunities available in India in this domain, the pressure remains on the industry to source skilled resources, resulting in competitive swapping of resources, leading to spiraling wages and nullifying the labor arbitrage that India has to offer. This can also lead to concerns from the pharma company's end, as this results in a loss of organizational knowledge and a duplication of training effort (thus extra costs) to the sponsor as well. Oversight would also be more complex, as this would include addressing different writing and interpretation styles, efforts to manage co-authoring, and training on multiple document types.[8] On the other hand, India has both a huge pool of trained medical professionals and PhDs, English is the language of business, and a fair number of professionals are trained on ICH GCP guidelines and have a fairly sound understanding of clinical trials.

To quote Helle Gawrylewski, Head Alliance Management, J&J PRD, Regulatory Medical Writing CoE, "Medical writing (MW) is not only about writing in a vacuum, but it's about being able to function well within a virtual team and make an impact. So we require written and verbal communication skills. I'm eager to see medical writing continue to develop into a respected and challenging profession in India and not be considered a stepping stone to management of writing groups or other types of work. Our reason initially to search in India for prospective partners for MW was based on the strong tradition of education and English language training in India. The strength of the talent pool and the potential there makes India an optimal location to place writing projects. Now we value not only scientists who can write but those who have the confidence to contribute their original scientific thoughts and critical assessments to what they write. Our partnership's overarching expectation is the creation of mutual value."

One of the ways of developing the medical writing community in India is the creation of the DIA India Medical Writing Working Group, which provides access to the proceedings of the global SIAC and ensures effective knowledge sharing between the two groups. Other methods would include establishing a Medical Writing Training Institute, which would address the industry's unmet need for skilled medical writing professionals. Further, as was the case with the CCDM certification for data management or SAS certification for SAS programmers, the implementation of the "International Medical Writer Competency Model," which defines competencies which yield superior medical writing performance, would help set benchmarks in our industry.[9]

Statistical programming is another domain where there is a clear supply-demand gap in terms of experienced resources. While there are a fair number of SAS programmers in the industry, clinical statistical programmers are still niche, and experienced resources in this category are few in number. Thus the availability of clinical expertise, the ability to move from transactional processing, such as the generation of TFLs (tables, figures, and listings), to actually creating the programming specifications, creating integrated summaries, and having a sound understanding of CDISC standards, can still be a challenge.

To conclude, India is and will remain a key destination for the outsourcing of these functions, and this industry will continue to grow. India has all the necessary advantages to establish itself as a leader, but the industry will need to work together to address concerns such as attrition and invest proactively in grooming skilled resources.

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14th Annual Workshop in Japan for Clinical Data Management

Makoto Yokobori

The 14th Annual Workshop in Japan for Clinical Data Management (CDM) was held on January 27-28, 2011 in Tokyo. There were approximately 350 attendees in the workshop from Japan, China, Korea, India, and all over the world.

Part of the workshop's title was "3D age." What does "3D" mean in the context of this workshop? It has nothing to do with 3D movies, of course. For this workshop, "3D" meant *data, diversity, and direction*. They have been important factors to CDM in recent situations, and this is the reason why we set the "3D age" as the theme.

The workshop started with two keynote addresses. The first keynote was "Principal Issues Now Facing Japan in New Drug Development and Expected Role of The Japanese Pharmaceutical Industry – From The Standpoints of Its Historical Background and International Position" presented by Dr. Tatsuo Kurokawa, Professor, International Clinical Development and Regulatory Sciences, Graduate School of Pharmaceutical Sciences, Chiba University. Dr. Kurokawa spoke about the current Japanese situation in the context of its history. He explained an economic outlook, trends in population, future vision for the health care industry, and the importance of an adequate quality level.

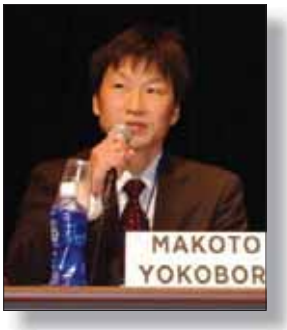
The second keynote was "Clinical Data Is Generated from The Patient – For Accumulating Clinical Data, Accurately and Efficiently" presented by Dr. Hiroyuki Furukawa, Professor, Director of Pharmaceutical Service, Yamaguchi University Hospital. Dr. Furukawa spoke about reality at medical sites. He noted the changes that had been implemented into sites, such as EDC. The shared message from two keynote speakers was the need for "adaptability to globalization."

The morning of second day was organized into parallel sessions. The standardization of CDM activities including CDISC and process evolution such as a new role for CDM were presented in Track A. Operational excellence in Asia that mentioned the current status of China and the new infrastructures were presented in Track B.

There were two afternoon sessions on the second day. One session was focused on ePRO (electronic patient-reported outcomes). ePRO has attracted a great deal of attention recently. Five presenters from the USA, Europe, and Japan discussed their experiences with ePRO. The other session focused on "Working Globally." Each presenter spoke about communication, outsourcing, and the effectiveness of using an electronic platform.

Because "global" and "Asia" are very important key words for Japanese data managers, attendees paid close attention to these presentations.

The workshop included a special program called CCS (CDM Chatting Session). CCS was held during the morning of the first day. This year, we had about 50 attendees. They were divided into seven groups, where they discussed their concerns regarding their daily work activities. The CCS symbolizes an outstanding feature of this workshop...attendees should not only listen; they should actively participate. The CCS, therefore, attracts many supporters who want to attend this session repeatedly. ■



***Mr. Makoto Yokobori** served as Vice Chair of the Program Committee.*

DIA, AHC & IFPMA Co-Sponsor 1st Asian Regulatory Conference

To help advance the regulatory aspects of various harmonization initiatives led by or in partnership with the International Council on Harmonization (ICH), the Asia-Pacific Economic Cooperation (APEC) forum, and the Association of Southeast Asian Nations (ASEAN), DIA will serve as co-sponsor for the Asia-Pacific region's first **Asia Regulatory Conference: Asia's Role in Global Drug Development**, to be presented April 26-28 at the Grand Hilton Hotel in Seoul, Republic of Korea. The APEC Harmonization Center (AHC) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) will also serve as co-sponsors.

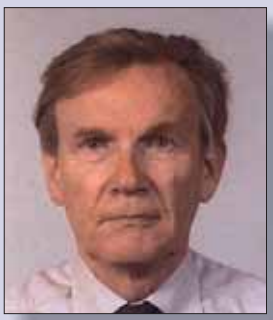
Asia's Role in Global Drug Development (DIA program #11910) will bring representatives from numerous Asian and ICH regulatory agencies together with professionals from industry and academia to discuss important aspects of good regulatory practices, good manufacturing practices, pharmacovigilance, global drug development, quality, and their implications for professionals who are considering initiating clinical research or regulatory activities in this region. Simultaneous translation in Korean will be available.

The conference program committee is chaired by Dr. André W. Broekmans (Vice President, Most of World Regulatory Policy & Regulatory Affairs, MSD, The Netherlands), who also serves on the ICH Steering Committee (SC) and Global Cooperation Group (GCG). Dr. Sun Hee Lee, Director, Drug Evaluation Department, Korea Food & Drug Administration (KFDA), and also a member of the ICH GCG, is serving as program committee co-chair. They will both chair the opening ceremony for this conference.

DIA President Elect Dr. Yves Juillet, Senior Advisor, LEEM (France) and also an APEC Harmonization Center Advisory Board Member, serves on the conference advisory committee. Prior to this conference, Drs. Broekmans and Juillet shared their thoughts about this program with the *Global Forum.*

Q&A Dr. Broekmans, why did you agree to serve as the chair of this program committee, and what does the committee hope to accomplish at this conference?

I believe in education and training as means of developing people and organizations. By providing opportunities to learn and to exchange ideas, we contribute to a better world. The ICH provides a framework of regulatory and development guidelines which also could be useful in important regions as Asia, in this way facilitating the access of important medicines to patients in need of them. The program committee offers a program with a diversity of topics of interest to the regulatory authorities, professionals in the pharmaceutical industry, and academia.



André Broekmans

Dr. Juillet, from your perspective as DIA President-Elect, why is DIA organizing this educational program with organizations such as the IFPMA, APEC, and the AHC?

A: Organizing this meeting is exactly in line with the mission of DIA, which is to provide a global forum, at an international level, that allows people who come from different organizations to work together to better develop, register, and survey new active substances. In this case, like many other DIA meetings, we will have the presence of representatives from the region's regulatory agencies, from industry, and from other stakeholders; because this is specifically a global Asian conference, we will host representatives of regulatory authorities from most Asian countries. It's really the first regional Asian regulatory conference that DIA has organized.

Focusing on our interest in partnerships, DIA has always been willing to develop partnerships with regulatory authorities and other organizations. This conference is a very good example of this type of partnership at the highest level: The APEC Harmonization Center is the organization that works on harmonization of regulatory requirements in the APEC region, which is very large and includes not only Asian countries but some American territories in proximity to the Pacific Ocean. IFPMA represents industry at the international level, and also provides the Secretariat of the ICH conference. We have here the key players, with DIA, in the organization of this meeting. When you look at the conference program, you'll see that this program is very well adapted to match the needs of these participants. ■

Yves Juillet

Three Years of DBS Experience & Implementation

Working to help our industry and regulatory constituents keep abreast of the latest scientific tools and technologies, our volunteer program committee continues to plan DIA's upcoming workshop on **Dried Blood Spot (DBS) Sampling in the Pharmaceutical Industry: Three Years of Experience & Implemention**, which will be presented May 3-4 at the Park Hyatt at the Bellevue in Philadelphia, PA.

Over the past several years, DBS on specialty papers has evolved as a methodology in the areas of pharmacokinetics and toxicokinetics, for certain study and molecule types. This upcoming workshop will provide an overview of best practices, underlying scientific principles, practical and pharmacokinetic implementation considerations, and explore case studies of DBS techniques and implementation, through podium and poster presentations from industry leaders in DBS sampling techniques.

Christopher A. Evans, PhD (GlaxoSmithKline) chaired DIA's first DBS workshop in December 2009, and returns to serve as chair for this year's program. He shared his thoughts on the continuing evolution of this technology and this workshop with the *Global Forum.*

Q&A This meeting will look back at "Three Years of Experience & Implementation" with DBS sampling. In the course of those three years, what has been the most pleasant surprise, and the most unexpected challenge or obstacle, in the implementation of DBS sampling?

The most pleasant surprise has been the amount of knowledge that we've gained around the technique and the technology. It seemed like a lot of people were initially standing on the sidelines, watching the technology, and that is no longer the case. Many organizations – CROs, pharmaceutical companies, even vendors – have really jumped into the cause, so to speak, and are actively investigating and using this technology. That's one of the most pleasant surprises. What the technology really needed was for others to start to use it, and begin investigating and experimenting with it, to further our collective understanding around DBS.

The journal *Bioanalysis*, for example, issued a call for papers for an issue dedicated to DBS. So many people contributed to this issue that it turned into two volumes. That's just wonderful, to see so many people actively investigating this technology; additionally, there are more DBS special issues planned for the future.

I don't want to say that this was an unexpected challenge because we did sort of expect it, but we're promoting a paradigm change, so one of the current obstacles is that because it is a new and novel technology, people have to change the way they think and more importantly, work. Some people embrace change and some people don't like, or have trouble adjusting to, change. Our obstacle is ourselves and our colleagues – convincing somebody that, in particular circumstances, DBS is a more appropriate matrix as opposed to liquid plasma. Additionally, as we research the technology more, we're starting to learn some finer details, discover things that we did not know, and identify areas that we don't have a good grasp on and need to investigate further. For instance, a recent challenge requiring investigation is the impact of hematocrit on DBS samples. This topic will be highlighted and discussed in depth at our upcoming symposium.

Another challenge that we're finding now is that since DBS are new and novel, we might question something around this technology that we might have taken for granted with plasma sampling. As we're investigating in blood spots, we look at something and wonder about its impact on plasma, and how we can account for this in plasma. That's kind of interesting.

Q&A Are there specific instances or study types for which DBS sampling should NOT be implemented and if so, why?

This is one of the things that we are learning: There are certain instances where DBS sampling is simply not appropriate. These instances can be attributed to particular study types, or are due to instability. We have never wanted to implement DBS throughout the entire clinical portfolio. Consider compound stability, for instance: Some compounds are simply more stable in cold conditions. We have identified, on a few occasions, where storage in plasma at -80° is potentially more stable than a DBS under ambient conditions. That's one instance.

Furthermore, if you have very high circulating levels of phase 2 metabolites, while your compound may be stable in the dried condition, the metabolite might not be, so the phase 2 metabolite can potentially convert back to parent in the DBS, resulting in an over-estimate of the actual concentration. It's another instance where we wouldn't want to use this technology.

Q&A What is the regulatory status of DBS sampling first in the US, and then elsewhere?

FDA is certainly aware of DBS. I don't know if it was on their radar three or four years ago but there is currently active interest in the technology. We understand that they're working on revising the bioanalytical guidance, and we're hopeful that the next guidance will include information about dried sampling and/or microsampling. The industry has engaged with FDA in a variety of forums recently, and has received some encouraging feedback, but nothing formal yet. That's something that we are eager for.

In Europe, specifically the UK, the Medicines & Healthcare products Regulatory Agency (MHRA) came forward to speak at the DIA meeting two years ago; they've also published an editorial, and have been very positive about the technology. From their standpoint, one of the primary advantages that we discovered around DBS was due to the three Rs with respect to animal sampling – the replacement, reduction, and refinement of animals in pharmaceutical research. Animal use is something that's heavily regulated and is of concern. The MHRA has stated very encouraging things: They would like people to investigate the use of this technology, and wish to be approached by companies who are interested in using it. I don't know the position of regulatory bodies relative to this technology in other regions, although I think it's something that they're starting to become interested in.

One of the other major advantages of DBS in the clinical environment includes the ability to use this technology in the desert, in a clinical trial around malaria, or for a drug in a developing world. To me, that would be key. I think there will be interest but I don't think that we've quite reached these regions yet, and aren't aware of the regulatory positions.

Q&A What "hot topics" illuminated at the previous DBS workshop will be reflected in the content of this year's workshop?

What we understand now versus what we understood even two years ago is simply unbelievable. Our conference will deliver a couple of presentations targeted at these fundamentals around DBS; concepts we did not have a full grasp on previously, but we're starting to research and understand now.

An unrealized "hot topic" at the time, is that essentially DBS is a "microsampling" technique – an ambient sample storage, microsampling technique. But here's what really got us thinking: We've identified certain therapeutic areas and classes where we want to keep with a plasma-based assay, so now we're starting to actively investigate areas for microsampling of plasma. Therefore, DBS has opened our eyes to microsampling in general. We're starting to identify a variety of mechanisms by which we are recognizing where plasma microsampling is deficient, so we're beginning to look at novel ways of microsampling plasma in both wet and dry forms (Dry Plasma Spots – DPS). I think that will be the next evolution of this technology: We've identified a new matrix, which is basically a microsampling technique, which we can now apply to all areas of sampling. There's another huge learning curve that we're about to go through. This technology can be applied to a variety of sample-limited matrices.

We even debated changing the name of this conference to include "Microsampling," but then we'd lose the "DBS" buzzword! ■

DIA Programs Help EMA & FDA Advance New ICSR

In May 2005, the International Conference for Harmonization released its revised Guideline (R3) for *Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs).* To facilitate the specification's wider interoperability across the global patient, health care, and regulatory communities, this was the first ICH technical specification to be collaboratively developed with Standards Development Organizations. ICH will define the way to use this standard by publishing an ICH Implementation Guide, expected sometime in mid-2011.

Working with the European Medicines Agency, DIA has facilitated two offerings to help patient care, pharmaceutical industry, and regulatory professionals in Europe prepare for its implementation: **European Medicines Agency Information Day: The New Individual Case Safety Report International Standard and ICH E2B** was first presented at EMA headquarters in London in June 2010, and will be presented again in London on 5 April. Working with the FDA for professionals in North America, DIA will team to present **FDA Information Day: The New Individual Case Safety Report (ICSR) International Standard and ICH E2B,** May 12-13 in Washington, DC.

The program committee for this North American offering includes Lise Stevens, Data Standards Project Manager, Office of the Commissioner, FDA, who previewed this "Information" and this "Day" for the *Global Forum.*

Q&A What are some of the Standards Development Organizations (SDOs) with whom the ICH Steering Committee will collaboratively develop technical specifications?

Lise Stevens

The SDOs approved by the ICH Steering Committee are the International Organization for Standardization (ISO) and Health Level Seven (HL7). However, The Joint Initiative on SDO Global Health Informatics Standardization (http://www.jointinitiativecouncil.org) created in August 2007 is a collaboration between several SDOs to collaborate and produce interoperable standards that reduce or eliminate current gaps, overlaps and counteracting standards within the participating SDO's existing programs. This is important for harmonizing other common industry-adopted standards developed by the Clinical Data Interchange Standards Consortium (CDISC), which is also a member of the SDO Joint Initiative.

Q&A What benefits do you anticipate this collaborative development will ultimately deliver to regulatory professionals? To industry professionals?

I try to think about whom we are really serving on both sides of this equation, regulators as well as industry. We are serving patients. That's why we're all here. The

number of global manufacturers of human pharmaceuticals and vaccines, including other regulated products, is decreasing due to mergers. These products are used worldwide and it is important that we all try to leverage, to the best extent possible, our infrastructure and reporting requirements so that the global manufacturers can realize economies of scale in meeting common international reporting requirements.

The Individual Case Safety Report (ICSR) standard is a great candidate for international standardization because of global interest in incorporating better patient safety measures in the whole continuum of patient care, which includes leveraging adverse event and public health reporting and incorporating that learning back into the overall health care system. The more that we can collaborate and share patient adverse experiences with global products, the better off we all are going to be because global regulators and industry can collaborate on better methods for producing products, and mitigating and communicating potential risks associated with the use of these products. Everyone can begin to realize better economies of scale in their infrastructure and business processes for managing reports and data sharing.

The other challenge that we should begin to think about is the opportunities that social networking applications are bringing into the area of patient safety and health informatics. FDA and industry meet on an annual basis to review progress in implementing electronic submissions and discuss best practices. A hot discussion topic is the development of social media applications for FDA adverse event reporting. We need to plan to accommodate a potentially large number of new consumer reports. The benefit of working within the SDO environment is that we can offer an internationally harmonized data exchange format that can be leveraged as these new technologies proliferate through the marketplace. iPhone applications, for example, can be configured to use the same data standards used by industry and regulators. This allows us to scale our infrastructure without the need to re-tool our investments each time a new technology emerges.

This is the motivation for promoting this specification. Any organization or person submitting adverse event reports, regardless of whether it is a consumer using an iPhone application, regulatory authorities exchanging information with the World Health Organization, or health care providers exchanging data, we all can use a common structure and eventually a common vocabulary for exchanging reports. We can begin to break down some of the barriers of data exchange and reconcile data from many different sources so they can be electronically accessed (eg, data mining), instead of combing over pages and pages and reformatting paper reports.

Q&A May we ask you to summarize the key differences between the forthcoming (R3) and current (R2) ICSR ICH E2B specifications?

The new specification improves alignment of many regional requirements into one common reporting guideline and submission format. We have incorporated better support for human vaccine products, and introduced additional product supply chain-related data elements such as global product identifiers, batch lot testing results, and discernment of counterfeit products. We improved the drug information section to better accommodate different drug/dosing therapies, eg, oncology drugs, and support for new Advanced Therapy Legislation from the European Union (EU). We were able to incorporate some of EU's requirements into the new exchange format without having to create something different, or a "one-off solution" just to accommodate the new reporting requirements. The ICSR specification includes structure to capture medical device information required for the new EU legislation, and support for combination product reporting. This is beneficial because those manufacturers producing combination products, where a device is one of the components, can essentially use the same reporting format to accommodate reporting for both drugs and combination products. The HL7 project team worked through FDA's liaisons to the Global Harmonization Task Force, which also had been working on a harmonized reporting guideline, to incorporate many of their device requirements into the specification.

Q&A What "takeaway" message do you hope to deliver to participants at this conference?

The primary message is that we all must embrace the power of health information technology and the efforts of ICH partnering with global SDOs to harmonize and design common data standards. These

standards facilitate longer term goals for data reuse, data sharing and safety analysis because we can leverage information received in disparate submissions. For example, the ICSR specification harmonized with many of the HL7 artifacts used for Structured Product Labeling (SPL), which is a specification adopted by industry to support drug labeling submissions to FDA. This is important because the information that FDA receives through labeling submissions, as well as new product registrations, can be used to help build global drug dictionaries. These dictionaries can be used to validate the drug information contained in the adverse event reports we receive. We now have a better way to validate if a product on the market is actually a regulated product with current marketing authorizations in the different countries in which ICH participates.

We are building and testing a new generation of standards that are more inclusive and promote a broader framework for supporting other over-the-counter, home use devices, and prescription products in the global market. The ICSR is a specification that provides the foundation for the realization of this goal over time. ■

European Perspective on New ICSR International Standard

Gaby Danan

Gaby L. Danan, MD, PhD (GLD Consiel, Pharmacovigilance Expert, France) serves on the program committee for DIA's upcoming *FDA Information Day*, and also serves on the program committee for the two *EMA Information Days* on this new ICSR international standard. He shared his thoughts on this standard, from his unique US/EU perspective, below.

Q&A What benefits do you anticipate that collaborative development of this international standard for ICSRs ultimately deliver to regulatory professionals? To industry professionals?

For regulatory professionals, the new ICSR should be viewed as an important harmonized tool for the detection, evaluation, and monitoring of suspected adverse reactions to medicinal products (ADRs) used in every country in the world. This unique message, containing all the information on ADRs, would facilitate their early detection and communication between all stakeholders in countries using this standard. For industry professionals, this standard would allow for delivering the same message content to all regulators according to their specific requirements. Ultimately, we expect it to increase patient safety and public health protection.

Q&A What "takeaway message" do you hope to deliver to those attending the EMA Information Day(s) on this new specification?

Be prepared to implement the new ISO/ICH ICSR message in your organization, because it will become the standard for ADR information exchange between all stakeholders.

DIA, FDA & PEI Co-sponsor 13th International Paul-Erlich-Seminar

Every three years, international scientific, regulatory, and industry, experts from around the world convene to discuss regulatory control and standardization of allergenic extracts at the triennial, International Paul-Erlich-Seminar. The most recent, 12th International Paul-Erlich-Seminar was presented in Bad Homburg, Germany, in 2008, and brought together more than 260 participants, including nearly 30 regulatory and government representatives, from 25 different countries.

Paul-Ehrlich-Institut

This year, DIA, FDA, and the Paul-Erlich Institut (PEI), have jointly co-sponsored the **13th Annual Paul-Erlich-Seminar: Allergen Products for Diagnosis & Therapy: Regulation & Science,** to be presented September 14-17 in Washington, DC (US). Dr. Harold S. Nelson (Professor, Department of Medicine, National Jewish Medical & Research Center; and Professor of Medicine, University of Colorado Health Sciences Center) will deliver the opening keynote address on *The History of Specific Immunotherapy (SIT) & Allergen Standardization;* the closing address will be delivered by Dr. N. Franklin Adkinson, Jr. (Professor of Medicine & Program Director, Division of Allergy & Clinical Immunology, Johns Hopkins Medicine, John Hopkins Hospital).

This seminar is also supported by the European Academy of Allergy & Clinical Immunology (EAACI) and the National Institute of Allergy & Infectious Diseases of the US National Institutes of Health (NIAID).

Dr. Ronald Rabin (Chief of Laboratory, Immunobiochemistry, Division of Bacterial, Parasitic & Allergenic Products, Office of Vaccines Research & Review, US FDA) spoke at the 2008 Paul-Erlich Seminar and serves on the program committee for the upcoming 2011 seminar in Washington, DC. He shared his thoughts about the past, present, and future, of this science and this seminar, with the *Global Forum.*

Q&A You spoke at the 12th International Paul-Erlich-Seminar in Germany in 2008. What hot topics discussed at that seminar have advanced into sessions that will inform this year's 13th international program?

RR: In 2008, we started to learn some of the mechanisms by which immunotherapy works. This meeting will have a little bit more of that. We've learned quite a lot about the immunological mechanisms of immunotherapy and of tolerance. That should be quite exciting.

Another quite interesting thing we began to hear about was characterizations of natural allergens, and how they might actually stimulate the allergic response. New data has been published on that just in the last couple of years. We have also scheduled a couple of very exciting talks on the inherent adjuvant biological and structural properties – two separate talks – of the natural allergens. That's very exciting.

In 2008, we started to hear about data from studies of recombinant allergens used at therapeutic agents that were just starting to come in; now, more of these studies are in their later phases, so we expect to hear some exciting data about that. Those are the basic stories that will be exciting to follow during this meeting.

Q&A For our readers who may be unable to attend, may we ask you to please preview the presentation you will make on the legal and regulatory status of allergen products in the US?

RR: My talk will deliver an update of some things that have changed as far as our regulation of allergens.

Actually, I would rephrase that to "some of the things that we've been thinking about and may be changing"– of course, that's a very important distinction in the regulatory world because we can't announce our changes in these meetings: We have to announce them within the context of legal documents, printed guideline documents, the Federal Register, and so on.

We are very much interested in making the testing of allergenic products less difficult in the US than it has been. I have delivered a few presentations that compare use of natural exposure to pollens – which is the typical way that this is done – to environmental chambers, and whether or not the FDA may accept data from environmental chambers, particularly in the context of phase 3 or pivotal studies. That's one large set of information in my talk.

The other is from a project that we are undertaking to replace an assay that allergists in the US and other parts of the world use to standardize two major allergens used in diagnostics and immunotherapy, ragweed and cats. Those are done, at least in the US, by an assay called radial immunodiffusion assay; this assay is laborious and difficult, and we've been setting up a different assay – the ELISA assay – to make it much more robust and, quite frankly, easier. These will be the main messages of my presentation.

In addition, Dr. Tammy Massie (Lead Mathematical Statistician, CBER, FDA) will discuss statistical considerations in proving efficacy in allergen immunotherapy for new therapeutics. Again, while she's not going to state any policy or anything novel, her talk is very important with regard to trying to demonstrate whether a product truly works and is effective in treating the symptoms of an allergy or not, because the scoring system that we use to grade these things is a clinical, subjective system: People either feel better or they don't feel better, and that's a lot more difficult than, for example, measuring blood pressure or cholesterol levels.

Q&A What "takeaway message" do you hope this conference delivers to participants?

RR: One of the things that I hope our attendees will leave with is a sense of excitement. We are now in a decade – at least a decade – to remember. This is an exciting time for immunotherapy in allergic diseases. Another important message is that we're all on the same page with understanding that this is a science-based endeavor and there's a lot that's exciting about the science, and we should all enjoy it.

The third message is particularly for those in the regulatory business of allergens, and for those in industry, and that's that we all have the same goal: We all want to bring effective products into the clinic, and make them available to those who would benefit from them. Sometimes we may agree or disagree about what needs to be done in order to get them there, but the unique aspect of this particular meeting is to create the understanding that we're not on opposing teams, if you will.

Q&A What did we not ask you, about this seminar or this topic, that you also wish to discuss?

RR: The only other thing that I would like to mention is how excited we are to be hosting and presenting this conference in the United States – it's an international conference that is usually presented in Germany – and how pleased we are to have the conference anchored by such luminaries in the field as Drs. Harold Nelson and N. Franklin Adkinson. This is really a terrific lineup of scientists, both from industry and academia, and regulators, and these have always been excellent meetings. It's been a pleasure to work with Dr. Vieths, who I only knew peripherally before we began working on this program together, and working with the professionals from DIA, who have been just that. ■

OPTIMAL BUSINESS TEAMS 1.0:
A Beginning Blueprint

Teams are a part of many aspects in life. Whether it is a professional sports team or children picking "sides" on the playground, the right people with enthusiasm can win the game—or even achieve the most extraordinary results like landing a space shuttle on the moon.

The same goes for business today. In the past, upper management executives oversaw the work of department heads—who subsequently supervised individuals. Currently, a predominant management style now features the team approach: with the assistance of a team leader, a small number of self-directed members work collaboratively to achieve agreed-upon goals.

For enterprises that use the latter approach, winning often depends on the capability of the leader, points out Jim Willis of Executive Edge, a team-building consultancy. "Team leaders who know how to adapt their leadership style as the team develops can help enhance the team's performance and create more positive results for the company." Based on research by the Hay Group, he extrapolates that a leader's ability can translate into as much as a 30% increase in business sales, revenue growth, efficiency, and profitability.

So what should executives about to embark on the team-building process know? What are the differences between departments and teams? What do company executives, team leaders, and team members need to know? To position a team for outstanding future success, it is important for these individuals to understand certain terminology and some basic business concepts.

The Home Team Advantage

Teams can help both businesses and not-for-profit enterprises in a number of ways.

In today's challenging economy, teams are being used to maximize existing talent. "Organizations set up teams in order to run leaner when there are just not enough resources," points out change-management expert Lawrence Polsky of PeopleNRG. This means an employee's talents are put on double duty. A "matrixed" employee carries out her usual responsibilities, reporting directly to one boss and serves on any number of project teams, informally reporting to team leaders, adds Nancy Settle-Murphy, owner of Guided Insights, a virtual collaboration consultancy.

Multifunctional project teams help achieve company objectives efficiently—and often operate within a hierarchal business structure. Business management consultant David Bowman of TTG Consultants reports that "time is saved and synergy created when project team members from diverse functions (accounting, research and development, sales and marketing, and manufacturing) are in the same room at the same time. "

Often, team members are able to solve problems quickly; usually, they have frequent and direct access to the end-user, as opposed to those in a "top-down" management style, points out Ed Pritchard of Everest Training and Consulting. Performance consultant John Brubaker in Maine concurs: This happened when salesmen—who interact directly with their accounts—shared customer feedback during a daily sales meeting. Team members were able to deduce that incorrect invoicing occurred when the company's head of

accounting did not inform the whole team about product price changes.

Teams vs. Departments

In addition to project teams, there are also intrafunctional teams with ongoing responsibilities, not unlike the sales situation above. Similarly, a company might establish a short-term ad hoc team consisting of a copywriter, graphic artist, media buyer, and advertising executive. These individuals could easily be grouped in a traditional department, as well.

However, you can't just take a department and call it a team, points out Pritchard.

An individual working in a department has discrete responsibilities and reports directly to a "superior." On the other hand, team members work in tandem and hold each other accountable for mutually dependent work tasks. And this egalitarian team becomes its own decision-making unit with the latitude to create its own methods of operating, including building a strategy to achieve the goal handed down by management.

In contrast, "a supervisor, such as a department manager, makes decisions, delegates, schedules work, and tells subordinates what to do, but a team leader demonstrates or coaches," explains Pritchard. And as Willis will further point out, an effective leader's authority should lessen as the team matures.

So what are some steps for setting up a successful business team? The process can be jump-started when those in charge keep their eyes open for talent early on. Anne Whitaker, Senior VP, Division Head, US Pharma at Glaxo Smith Kline points out that this happens frequently at her company and new hires who seem to have "innate leadership ability" are given special training courses.

This is where team building can officially begin.

Step One: Decide Who Should Lead

Whitaker says team leaders "are naturally able to influence their peers as well as those at all levels in the organization, especially in challenging situations." She relates that they also "develop strong interpersonal relationships and business solutions, and are flexible thinkers." They also play the roles of "change agent and coach," she says. Pritchard, meanwhile, points out two other important attributes: "Team leaders need to give and receive feedback, and be part of the team process. 'Jim,' a former supervisor in a manufacturing firm, illustrates the latter. When his department became a team, 'Jim' moved his desk from a front office to an office near the plant floor. He could then work in close proximity with his team members in the production process."

Here is perhaps one of the most critical criteria for those in charge: An astute leader must be able to decide whom to bring onto the team. As Whitaker puts it, "Every team needs the right leader to drive the team forward, to pick the right people to put on the team, and to make appropriate assignments to get the most from all members of the team."

Step Two: Choose the Team Players

Here are some tips for those who need to make these important decisions:

- For the team to succeed, each member must carry his own weight. That's why it is so vital that each interdependent member be highly competent in his functional area. Then, other members will feel confident to "throw the ball to his team mate," according to *The Orange Revolution* by Adrian Gostick and Chester Elton.

  How can team leaders ensure that candidates possess the requisite ability? "Assuming that the work history and references check out," offers Settle-Murphy, "you can also devise well crafted questions to hypothetical team situations. For example, *If you are a team leader with a tight deadline, and a key member unexpectedly leaves at a critical time, what's the first step you might take?* A capable candidate should be able to provide insightful off-the-cuff responses."

- Make sure that you choose a variety of people with all the distinct competencies needed to perform team activities, offers Polsky, who adds that the resulting team should ideally contain personalities with diverse views and opinions.

- In addition to their given functional area, Baltimore, Maryland, business consultant Joni Daniels advises that

TEAM MEMBER TIPS

- Listen to the ideas of others
- Be open to change
- Contribute your past experiences
- Initiate ideas for the group
- Ask questions to get clarifications
- Reach out to teammates outside of work
- (What are their non-business interests?)
- Become an unofficial team leader
- Get ready to brainstorm to benefit the team

it strengthens the team if members also possess other abilities, such as Internet research, oral presentation, and writing skills along with innate organizational abilities.

- When choosing team members, consider each candidate's skills, and who she is as an individual and her many aspects, regardless of age. Refrain from making generalizations about the generations. "At the same time, it is also important to understand generational learning styles because they give us insight into how people work and learn," offered author Gina Gotsill, co-author, with Ken Ball, of the book *Surviving the Baby Boomer Generation—Capturing Knowledge for Gen X and Y Employees.*

- Bowman suggests using human resource assessment tests to uncover each candidate's style of learning, personal interaction, and socialization; Kent Greenes in the above book asserts that "it is just as important to understand generational learning differences as it is to understand personality traits." Anne Thornely-Brown of Oasis Executives, a team-building consultancy agrees. She has already seen "swift and dramatic changes in how individuals behave and perform in team settings based on their age bracket." (She feels the effect will become more dramatic as individuals aged 25-35, with a more spontaneous lifestyle and a preference for electronic communications, begin to take on the majority of team leadership roles.)

Step Three: Conduct One-on-One Interviews

The members of "breakthrough teams" possess three common characteristics or "breakthrough traits," according to a recent research study cited in *The Orange Revolution* by Gostick and Elton. Team members at 21 top companies such as Zappos, Whirlpool, and Pepsi, were all "highly self-motivated and engaged (trait #1) —with a commitment to doing their very best for themselves, their team and the company."

Since this first breakthrough trait is so important, Gostick suggested, in a phone interview with the *Global Forum*, that team leaders ask candidates face to face: *"What is your value system? What is important in your life? What are your goals at work? What drove you forward in your previous job?"*

Experts agree that it is crucial to harness this drive to benefit the team. And once this trait is uncovered, the team leader "Bill" should offer to help, continued Gostick. If "Jill" reveals she really wants to get on the management track, "Bill" should help promote her ambition, realistically, with a give-and-take attitude. "Bill" might suggest: 'I will give my commitment to do all I can to get you on the management tract. That honestly may take a year or two. What I ask in return is that you give me a full 100 percent every day that you work for me. Can you commit to that?'"

This type of conversation can lead to the related engagement process, says Daniels. This occurs, she explains, "when leaders create meaning in everyday work, by correlating what is important to team members." Willis says that these engaged individuals "bring out their very best interpersonal skills, individual competencies and subject expertise to bear on the task." They also "go beyond expectations to contribute to the team and to the well-being of the enterprise at large," concludes Darelyn Mitsch of Pyramid Resource Group.

Step Four: Hold an Introductory Kick-Off Meeting

During the first of several introductory group sessions, leaders can promote open communication and trust. This is the second "breakthrough trait" according to *The Orange Revolution*. As members meet for the first time, leaders should moderate discussions where members "share information and past experiences," relates Daniels. She and Thornley-Brown agree a discussion can be centered on the following, or similar questions: *"When on previous teams, what were the goals; what worked? What didn't? What would you have done differently?"*

While some individuals may hesitate to participate, team leaders need to gently urge them to speak about past experiences, advises Polsky. "If not, trust can't be established. Later on, they will feel vulnerable and be afraid to make mistakes. They will avoid making decisions, which is vital to a strong team."

Here's another crucial meeting objective: these conversations should mobilize the team to begin productive thinking on how to reach the goal set by management (such as, increase sales revenues by 5%; or oversee an advertising budget of $x for each fiscal quarter next year). Strategy development will take place later, but Gostick advised that "in order to incorporate trust and collaboration around this issue, the team leader should assure members in a non-authoritative manner: 'I am going to lead the effort, but we all are going to be accountable for hitting the goal and I'm going to need everyone to own their part.'"

Step Five: Engage in Team-Building Activities

When team members "support, recognize and appreciate each other" they create "camaraderie or esprit

INITIATING TEAM DYNAMICS IN A VIRTUAL TEAM

Provided courtesy of Nancy Settle-Murphy, owner of Guided Insights, a virtual collaboration consultancy, unless otherwise noted.

"The very best way to create trust is to arrange an initial in-person kick-off meeting. It is essential for teammates to meet face-to-face because without that interaction it will take much longer to develop the kind of trust needed to achieve team goals in a timely manner. If this step is skipped, the team will take far longer to get work done."

If cost and logistics or other factors absolutely prohibit an in-person "kick-off," arrange for an in-person meeting of core individuals. Then create a subsequent "virtual kick-off meeting" of all members using virtual communication tools that include a visual component. Anne Whitaker, Senior Vice President, Division Head, US Pharma at Glaxo Smith Kline, who once headed up a global team, recommends using a Webcam and video conferencing to show what team members and their environments look like. Afterwards, "phone team building sessions" can help team members get to know each other, says Settle-Murphy.

Remote teams have successfully built camaraderie through the use of logos. The symbol has created a sense of unity when inserted at the bottom of each member's email signature, as an electronic header on virtual collaboration tools, and on apparel.

de corps"—the third and most vital trait of *The Orange Revolution's* "breakthrough teams." Brubaker says, "There is no better way to build this—in addition to trust—than by having members overcome shared adversity through a structured team-building activity." If the members are physically fit, this can be accomplished on a specially designed "ropes course." While wearing a harness, members maneuver on the ground or in the air to reach game goals set by a team-building coach. "Each member's actions can reveal his personality traits, problem-solving abilities, and potential team roles. And during a mandatory follow-up discussion, the exercise should be used as a metaphor; then members can begin to define how they can successfully contribute to the team."

To the same end, team leaders should provide additional ongoing structured interpersonal opportunities. Mitsch suggests asking each member to describe a game he or she enjoyed as a child and tell a story about it. This will help each team player to:

- articulate how he contributed to other teams (in a word or phrase)
- provide examples of his strengths outside his functional area: (mathematical skills, fundraising, or problem-solving skills)

Leading with Style

As Willis points out, for the group to succeed, the leadership style must change as the group develops. At this first phase of the process—which is called the "forming stage" according to Bruce Tuckman's 1965 team development model—Willis reports that a "directive style" is appropriate. That's because the team leader at this critical juncture "guides the formation of positive relationships…with expectations of what the team is going to accomplish."

Willis says it is appropriate for the leader to act in a traditional authoritarian manner, "while being open to members' input—while members listen and ask extensive questions."

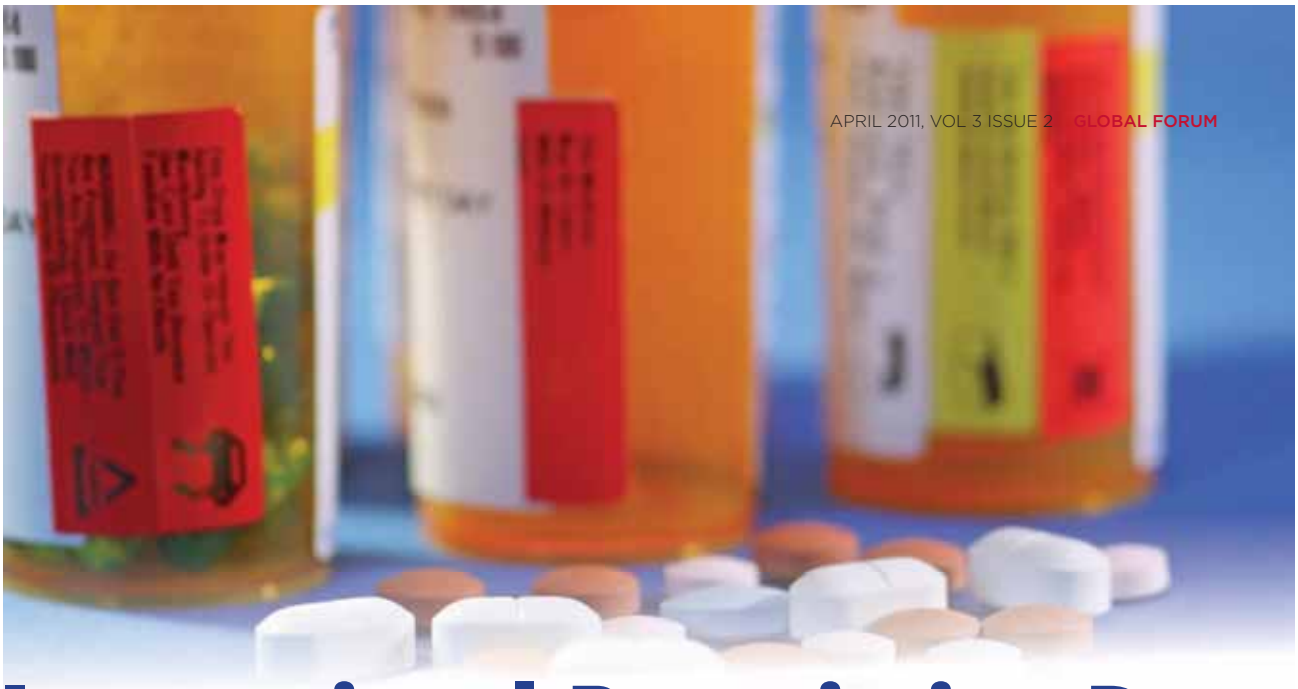
As the team building continues, the team leader "Bill" will use experience and intuition to switch to a coaching style in Tuckman's next team development phase, and to gradually relinquish authority. "Bill" will get his cues as team members share their histories and ideas (forming camaraderie) —and as others put these ideas into action—to become unofficial group leaders.

NEXT STEPS: BUILDING FROM THE BLUEPRINT

Now that we have the team set up, what will await the members? Team members will:

- form the team's operational guidelines (how to handle conflicts, communications and decision-making)
- brainstorm innovative ways to reach the final team goal (strategy development)
- determine what roles the members will play
- set the completion dates

Learn more about team dynamics in our next installment "Business Teams 2.0." ■



International Prescription Drug Labeling Conference

This past December 8-9, approximately 150 attendees joined DIA and regulatory authorities from Canada, the European Union, Japan, and the United States, to attend a conference entitled **US & International Prescription Drug Labeling: Comparisons & Important Updates** at the Embassy Suites DC Convention Center in Washington, DC.

On December 7, an optional preconference tutorial with 4 modules was held: One to address the EU Product Information Management (PIM) electronic labeling system, and one to update the attendees on the implementation of US Structured Product Labeling (SPL) and the use the electronic listing system (eList). The FDA also held a tutorial on writing the Highlights Section and one on writing various safety sections of the Full Prescribing information. Approximately 60 participants attended these four workshops.

The following two days consisted of presentations by individuals from regulatory agencies in Canada, EU, Japan and the US. They reviewed the content and format requirements for several sections of health care professional labeling (the Indications, Adverse Reactions, Warnings and Precautions, Interactions, and Clinical Studies) and key requirements for patient labeling.

The conference concluded with two "Hot Topics" sessions, offering the regulatory agencies from Canada, European Union, Japan, and the US the opportunity to provide information on important labeling initiatives, developments, and updates.

Steven W. Bass, PhD (Bass BioPharm Consulting Group, LLC) and Dr.med Leander Fontaine (Pharmiceutics, LLC) both served on the conference program committee and shared these reflections and perspectives with the *Global Forum*.

Q&A What was the background and purpose of this labeling conference?

SB: Members of the DIA Labeling Working Group of the Regulatory Affairs SIAC had indicated to Leander and me that it would be a great idea if we could have regulators from various countries present a "hands-on update" on physician and patient labeling. This had never been done before, so we took this as a challenge and began to discus this with DIA and various regulators. I guess the time was right since there was great interest from each of the agencies we contacted to move ahead with this concept. About a year ago we began to have a series of telephone conferences with regulatory and industry members of the program committee from Canada, EU, Japan, and the FDA. They all worked with us, week after week, to share their thoughts and put this very comprehensive and, I feel, extremely successful conference together. The regulators also worked closely with us to prepare a series of tables that provided for a side-by-side comparison of their positions on key labeling questions and issues.

Q&A What were some of the primary "takeaways" that participants brought back to their workplace from this conference?

LF: In my view, the most important output of this conference was this set of comparison tables and the accompanying structured

presentations through which presenters answered a large number of questions, addressing issues frequently encountered by labeling people in industry. There were about 60 such questions and topics, some of which were rather involved and required our regulatory presenters to caucus among themselves before answering. So, many of their answers were not simple recitations from guidelines or regulations. The answers we received will influence how industry approaches local labeling documents for these agencies. And they will help us craft Core labeling that is easier to implement.

What we see on these comparison tables is a high level of similarity between the regulatory positions held by these agencies. Obviously, there are still differences in how agencies approach the specific content and structure of local labeling. However, with respect to, for example, the selection of adverse reactions and interactions that go into labeling, we see them rather well aligned.

Q&A What other information will be useful to industry and regulatory attendees?

LF: From an industry perspective, this conference was also a chance to make the agencies better understand issues we face and questions we have when composing labeling, and safety labeling in particular.

Another key takeaway for me is that FDA is becoming increasingly strict in insisting on compliance of proposed US labeling with applicable regulations.

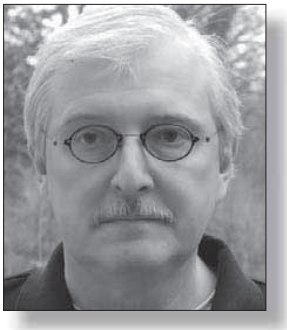
SB: FDA expects industry to fully comply in proposed labeling with format as well as content requirements, and they're going to be looking at submitted labeling earlier, as opposed to later, in the review of an NDA or BLA. FDA is also looking at its own labeling review process, and is obviously concerned with not only format but also with optimizing content.

Q&A May we ask you to share one more thing that you'll remember from this conference?

LF: I will always remember the passion for good labeling all agency presenters showed during the preparation for and while at this conference. And the great collaboration we had among both agency and industry representatives on the program committee with the objective to make this the outstanding labeling conference it became.

SB: It's very important that we clearly recognize the extensive preparation and effort made by the regulatory agencies and their presenters to prepare the slides and to populate the comparison tables that formed the backbone of the sessions. Without this commitment we could not have shared so much valuable information as well as updates on important developments and initiatives that are underway. ■

Steven Bass



Leander Fontaine

From March 8 through April 5, DIA offered a five-part webinar series that presented a special online version of our 2010 **US & International Prescription Drug Conference:** *Safety Information in the Canadian Product Monograph: Writing the Adverse Reactions, Warnings & Precautions, Contraindications, and Drug Interaction Information* (Webinar #11212); *Safety Information in the EU: Summary of Product Characteristics* (#11213); *US Prescribing Information: Writing the Highlights* (#11214); *Safety Information in the US Prescribing Information: Writing the Adverse Reactions, Warnings & Precautions, Contraindications, and Boxed Warning Sections* (#11215); and *Safety Information in Japanese Prescription Drug Labeling* (#11219). You will soon find all five parts available as "Archived (on demand) Webinars" in the "Online Learning" section of our **www.diahome.org** website.

FDA/EMA Announcement Concludes CMC Workshop

In February, DIA presented our biennial **Chemistry, Manufacturing & Controls (CMC) Workshop** at the Washington Hilton Hotel in Washington, DC. This year's workshop, **Translating Science into Successful Regulatory Submissions,** was developed by the CMC Working Group of the DIA Regulatory Affairs Special Interest Area Community (RA SIAC) with the American Association of Pharmaceutical Scientists (AAPS) as co-sponsors, and was attended by approximately 250 total participants.

Consisting of plenary lectures and breakout discussion sessions, this workshop addressed science- and risk-based approaches to drug development and manufacturing, setting specifications, stability topics, and postapproval changes, along with their associated implementation and regulatory challenges.

At the conclusion of this workshop, FDA Office of New Drug Quality Assessment Director Dr. Moheb Nasr and European Medicines Agency Quality Working Party Chair Dr. Jean-Louis Robert jointly announced a new step down the harmonization pathway: A pilot program for their agencies' joint review of the quality-by-design component of new drug marketing applications. It was explained that this joint review will not apply to the whole application file but to the part relevant to quality by design (development, design space, real time release testing, etc). The first step of this pilot will include only chemical, and not biological, entities, and will encompass new drug applications, supplements/variations, and scientific advice. Participation from companies prepared to simultaneously submit filings in the US and EU will be voluntary. FDA and EMA officially announced this new pilot program on March 16.

As chair of the CMC Working Group within DIA's RA SIAC, Yasmin de Faria Krim, PharmD, MScRA (Johnson & Johnson, Belgium) also served as program chair and delivered the welcoming remarks for this workshop. She shared her thoughts on it with the *Global Forum*.

Q&A This workshop featured both plenary and breakout, cross-functional discussion sessions. How were topics organized into these different types of sessions?

Yasmin de Faria Krim

Although it did include both plenary and breakout sessions, the workshop was mainly presented in four parts, covering quite a lot of topics through 20 sessions in total.

The first part began with a plenary session focused on such important topics as ICH Q8, 9, 10, and Q11, followed by parallel sessions that related back to these primary topics.

The second part was dedicated to analytical issues, which began with plenary sessions on setting specifications and on stability, followed by three parallel sessions related to analytical topics such as genotox impurities, global stability studies (with a focus on Brazil), and also harmonization of compendiums. The third part covered CMC documentation for clinical trials (chemicals and biologicals), audits/inspections, the Asean CTD, and combination products.

The fourth part, presented on the final morning of the workshop, was dedicated to post-approval: A plenary session featuring EU and US perspectives, followed by three parallel sessions – one dedicated to CMC postapproval plans, and two other sessions dedicated to post-approval changes in the EU and Canada.

These four pieces provided the backbone or skeleton of the entire workshop, which presented subjects

that are now and will continue to be topics of interest.

How did co-sponsorship by the American Association of Pharmaceutical Scientists add value to this workshop?

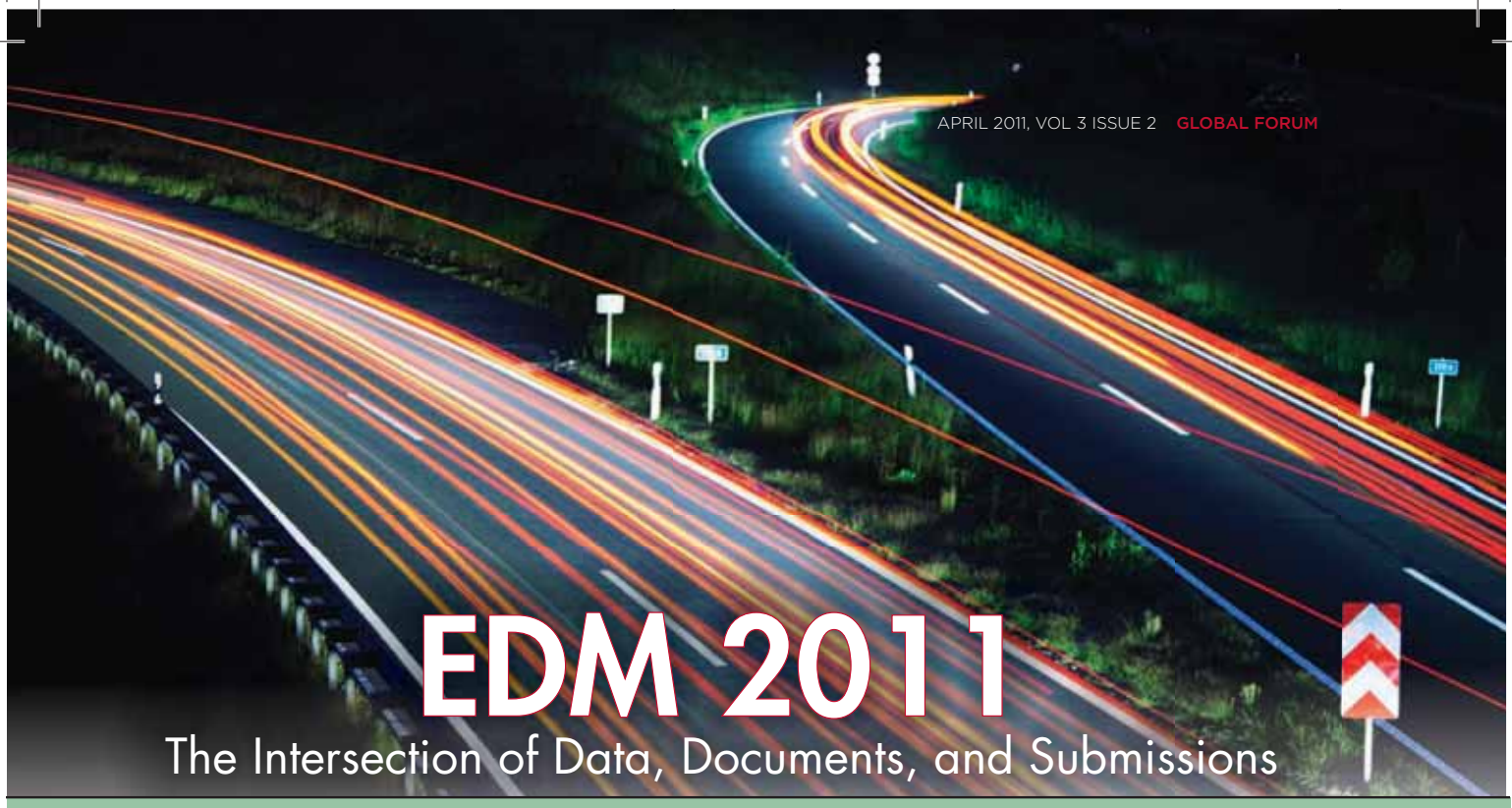
Our program committee included representatives of industry, regulatory agencies, DIA members, and AAPS members. DIA partnered with the AAPS for the 2009 DIA/AAPS CMC Workshop in Bethesda, Maryland. This workshop and partnership proved so beneficial to both organizations that it seemed quite logical to repeat the experience at this 2011 workshop. This workshop, like so many other DIA programs, featured strong participation from the regulators' side, including representatives of the FDA and European Medicines Agency on the program committee. Working with AAPS enabled us to explore more deeply the scientific side of CMC.

From your perspective as program chair, what was the most satisfying result of this workshop?

The way that we heard from attendees about how much they enjoyed it, along with the way that the attendees so actively participated and asked so many interesting questions during our sessions. I am more accustomed to being a workshop attendee than a workshop chair, and am happy when I choose a good workshop or training course or conference to attend. Thus, it was nice to see that participants were satisfied with the content of the program and the many topics covered. Some participants commented that they were glad to see that also non-ICH topics were presented.

What are your hopes for the next biennial DIA CMC Workshop in 2013?

I hope we can continue to bring together more speakers from even more diverse countries or regions. Our recent workshop included attendees from Japan, from South Korea, and from India, and our presenters included speakers from Brazil and Singapore. There have been many requests to present this DIA CMC Workshop in Europe, too. ■



EDM 2011

The Intersection of Data, Documents, and Submissions

DIA's electronic document management (EDM) conference was held on February 15-17 at the Gaylord National Resort and Convention Center in National Harbor, Maryland. With approximately 250 attendees and 42 exhibit booths, this year's conference continued the 23-year EDM tradition of serving as a forum for the discussion of emerging standards and the processes for the creation, submission and retention of regulatory information. This year's program was enhanced to provide a more comprehensive and interactive experience.

Tutorial Day was held on February 14, with four concurrent preconference workshops offered on Optimizing Trial Master File Efficiency through Implementation of the Trial Master File Reference Model, Why Do We Need a Taxonomy?: EDMS and Metadata, Guidance-compliant eCTDs, and eCTD onboarding.

Paul Pomerantz, DIA's Worldwide Executive Director, delivered the opening remarks, welcoming the attendees and presenting representatives from the EDM Reference Model and the TMF Reference Model with recognition plaques.

Paul was followed by the keynote speaker, David Miller, Chief Security Officer, Covisint, who spoke about "Document Access Management in a New Century: What the Pharmaceutical Industry Must Do to Avert Its Own WikiLeak Disaster." In his keynote presentation, David outlined the unique challenges of industry-wide collaboration, and shared the necessary strategies for properly managing control in large complex ecosystems.

Following the opening remarks and keynote address, the conference got underway with three parallel tracks running throughout all of day 1 and the morning of day 2. On the afternoon of day 2, two regulatory update sessions were presented, followed by an FDA Town Hall session. The three parallel tracks resumed for the morning of day 3.

After a number of discussions during the EDM conferences, two successful working groups were formed, the Trial Master File group, comprising members of the Electronic Regulatory Submissions and the DRM, SIACs, and the EDM Reference Model for Regulatory Submissions group, composed of members of the Documents and Records Management SIAC.

The Trial Master File (TMF) Reference Model officially began in February 2009, as a branch of the EDM Reference Model, under the co-leadership of Lisa Mulcahy and Karen Redding. The goal of the group was to create a model for TMF content, naming, structure, and basic metadata which can be used and adapted by any sponsor running clinical trials. Creation of the TMF Reference Model has involved more than 170 representatives, from more than 120 biopharmaceutical companies, contract research organizations (CROs), consultancies, technical vendors, industry groups, health care, academia, not-for-profit/NGO, and regulatory agencies. Version 1.0 of the model was released in June 2010, which then underwent widespread review, including review by the MHRA and the FDA.

Version 1.1, incorporating these review comments, was released on 9 February 2011.

The uptake of the model has been phenomenal and widespread. This model is a reference for the industry and should not be considered mandatory, but rather an opportunity for standardization across the industry. The TMF Reference can be adapted to an electronic or a paper TMF.

The EDM Reference Model for Regulatory Submissions began development in February 2008. The working group was comprised of members of the SIACs for Document and Records Management, Electronic Regulatory Submissions, and Medical Writing, including sponsors, consultants, and vendors. The Regulatory Submissions group focused on the content taxonomy and metadata requirements in support of CTD/eCTD submissions, designing the model to be vendor- and technology-neutral. The model targets the regional/administrative, quality/CMC, nonclinical and clinical components of Modules 1 through 5. The Regulatory Submissions reference model was first released in autumn 2008, and was distributed to over 40 EDMS and publishing vendors for feedback, with version 1.1 released in June 2009, comprising the Reference Model spreadsheet and user guide.

The next major version of the Regulatory Submissions Reference Model is in development to harmonize with the TMF Reference Model, and to extend the model to a greater breadth of global requirements, as well as deeper representation of supporting (non-submitted) content for Modules 1 through 5.

Additional working groups are being launched to add reference models for Prescribing Information and for Drug Safety/Pharmacovigilance/Risk Evaluation and Management Systems (REMS).

A number of EDMS and submission publishing vendors have endorsed the Regulatory Submissions Reference Model and are offering products configured for the artifact names and metadata recommendations of the model. The Regulatory Submissions reference model is increasingly requested in sponsors' requirements for new EDMS and publishing systems. ■

SAVE THE DATE

The Electronic Document Conference 2012 will take place January 31 – February 2, 2012 at the Hilton Baltimore, Baltimore MD. A call for abstracts will be available on the DIA website in June 2011. Three quarters of speakers for this conference are chosen from abstract submitters.

FDA Webinars Focus on Safety & EDC

In February, FDA presented two online seminars that refined and advanced discussions on hot topics regarding pre- and postmarketing safety, and on the Agency's Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations issued in January 2011, through two webinars facilitated by DIA.

CDER Town Meeting: Safety Hot Topics (#11206)
February 8, 2011

Webinar Moderator:
Sandra L. Kweder, MD: Deputy Director, Office of New Drugs, CDER, FDA

Presenters:
Toni Piazza Hepp, PharmD: Associate Director for Regulatory Affairs, Office of Surveillance & Epidemiology, CDER, FDA

John K. Jenkins, MD: Director, Office of New Drugs, CDER, FDA

Claudia B. Karwoski, PharmD: Director, Division of Risk Management, Office of Surveillance & Epidemiology, CDER, FDA

Sandra L. Kweder

Developed and presented by representatives of the FDA Office of New Drugs and the (CDER) Office of Surveillance & Epidemiology, **CDER Town Meeting: Safety Hot Topics** was modeled as an online version of the CDER Town Meeting that perennially highlights DIA's Annual Meeting. "Hot Topics" were defined as topics about which CDER has received many questions, or topics which have substantially evolved within the past few years. Attendees were able to submit questions in advance via email, or during the webinar through the webinar's interactive online chat function; after the panel's presentations, the concluding Q&A session was based on these audience questions.

FDA has developed separate rules for pre- and postmarketing drug safety. The premarketing rule was published in September 2010 and became effective in March 2011. Dr. Sandra L. Kweder reviewed the clarification and resolution of confusing terminology from the previous rule for safety reporting requirements (proposed in 2003) along with a more comprehensive definition of sponsor and investigator responsibilities for reporting serious and unexpected adverse reactions through safety reports for Investigative New Drug (IND) applications, bioavailability or bioequivalence studies, and investigator reports, in this new premarketing rule.

Other definitions refined by this new rule include what the presenters called the universe of adverse events:

- An *adverse event* is any untoward medical occurrence associated with the use of a drug in humans *whether or not considered drug related.*
- A *suspected adverse reaction* is an adverse event for which there is a *reasonable possibility* that the drug caused the adverse event; "reasonable possibility" means that there is evidence to suggest a causal relation between the drug and the event.
- An *adverse reaction* is a suspected adverse reaction with a much higher level of certainty about this causal relation.

This new rule also implements internationally harmonized reporting standards for the purpose of eliminating reports that generate a lot of paper without a lot of value. FDA and investigators should receive fewer individual reports, but the reports they will receive should be more complete and meaningful.

Toni Piazza Hepp and Claudia B. Karwoski led the presentation on the *Postmarketing Safety Reports for Human Drug & Biological Products: Electronic Submission Requirements* rule, which requires all postmarketing safety reports to be submitted in an electronic format that the Agency can process, review, and archive, proposed in August 2009 and still being finalized at the time of this presentation. They also provided an update on implementing Risk Evaluation & Mitigation Strategies (REMS) based

on comments heard at the July 2010 FDA public meeting on REMS. The overall objective, they explained, is to develop standardized REMS that can be "plugged in" to existing health care systems and yet simultaneously address specific risks.

Topics during the Q&A period included FDA recommendations for how frequently to perform literature searches, recommendations for additional clinical trials to evaluate cardiovascular risk, and how FDA internally tracks resolved and unresolved safety issues.

FDA's Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations (#11208)
February 28, 2011

Webinar Moderator:
Stephen E. Wilson, DrPH, CAPT, USPHS: Director, Division of Biometrics III, CDER, FDA

Presenters:
Jonathan Helfgott: Consumer Safety Officer, CDRH, FDA

Bhanu Kannan: Consumer Safety Officer, CBER, FDA

Leonard Sacks, MD: Acting Director, Office of Critical Path Programs, Office of the Chief Scientist, FDA

Matthew Thomas, MD: Health Science Administrator, Office of the Commissioner, FDA

Stephen E. Wilson

During the webinar on **FDA's Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations,** representatives of the FDA eSource Guidance Working Group and other agency leadership shared their "inside the agency" perspective on this draft guidance, which was in the docket for public comment until April 7.

The presenters began by explaining the shortfalls of paper source documentation (most notably potential transcription errors), the benefits of using electronic platforms and source documentation, and the subsequent need for corresponding guidance. Electronic platforms can prompt for missing data, deter the input of fabricated data, and provide the ability to input data at the same time is collected.

Presentations divided electronic data capture (EDC) on the electronic Case Report Form (eCRF) into three tiers – data collection and entry, data review, and data processing and transmission – and then summarized the benefits of processes within each tier. The data collection and entry process overview included definition of data element identifiers, pieces of electronic information linked to every data element that capture the originator of the data, the date and time the data was entered into the eCRF, and the study subject to whom that data belongs. They also walked through the Agency's preferred approach for modifying and correcting previously entered data.

Electronic platforms for clinical investigations have enormous potential advantages that will result in improved clinical trial quality and safety, the presenters concluded. Perhaps the most significant benefit of the eCRF is its ability to integrate data such as x-rays, CAT scans, and other images, a tremendously important advancement.

Stephen introduced the concluding question and answer period by noting the benefits of presenting this webinar while the public comments period was still open, because these interactions help inform the Agency of what they must do to finalize this guidance. Questions included one that the agency hears quite often: Can a sponsor host eSource data? (There is no specific regulatory requirement against this, but it can be difficult to maintain compliance.)

Monitor www.diahome.org for upcoming webinars as they become available and archived webinars that have already taken place.

2011 Board of Directors Election

This year's election will run through the month of April and includes an excellent list of candidates to join DIA's Board of Directors.

Election Process

All eligible members will receive an email link to review election information and vote via DIA's certified election partner, VR Elections. This allows members to make their voices heard with every assurance of complete confidentiality.

The DIA Board of Directors is the steward of the DIA Mission and Vision, and provides strategic planning, fiscal oversight, and leadership for the future of the association. Please take a few minutes to vote when you receive your emailed voting link.

How Are Candidates Selected?

The Governance and Leadership Committee of the DIA Board of Directors chooses the slate of candidates based on the Call for Nominations. Each year, the Committee examines the makeup of DIA's membership and tries to ensure that the candidates will continue to provide a balanced representation of DIA's constituents. In addition to experience with DIA, the Committee must consider the demographic and geographic distribution of candidates who may be elected to join the Board, as well as diversity of potential candidates.

Final Slate of Candidates

Nominee for President-elect:
Ling Su, PhD

Nominees for Director:
Deborah Dolan, BSN, MBA
Michele C. Livesey, BS, MBA

Nominees for Director:
Judith L. Glennie, PharmD, MSc
Sandra Milligan, MD, JD

Nominee for Director–Regulatory Authority:
Sandra L. Kweder, MD

Nominee for ACNA Chair :
Jennifer L. Riggins, PharmD

Nominee for ACE Chair:
Beat Widler, PhD

Announcement of Voting Results

The results for the 2011 election will be announced in June during a membership meeting to be held prior to the start of DIA2011 in Chicago and announced in a subsequent issue of the *Global Forum.* ■

Keep Your Eyes on Your Inbox. Your voting link will be emailed to you

Driving Online Learning in Business

Carrie McKeague

The winter of 2010-2011 has earned its place in the US weather records. Shuttered trains and buses, thousands of canceled flights, and impassable roads have stranded people from New England to Southern California. Caught between harried parents and cranky vacationers were business travelers. Some of them were hunkered over their laptops, PDAs, and cell phones, conducting business despite the breakdown in transportation.

The business people traveling to onsite training or education programs were out of luck. For them, and for their employers, the delays translated into lost time and expenses that delivered no value.

Saving Time and Money

The time and travel costs of centralized, instructor-led corporate training led to the early adoption of online training in the business world 20 years ago. Although the need to optimize productivity and control costs continues to drive companies, the factors hammering at company bottom lines in 2011 are more complex and demanding than could have been imagined in 1990. Online training is helping companies and individuals deal effectively with the challenges and opportunities of today's business and professional world.

The global business of 2011 is dispersed, decentralized, and knowledge-based. In fact, the factors that fueled earlier waves of globalization have been turned on their heads. Countries once dismissed as "developing" now offer workforces of highly skilled scientists, researchers, and medical professionals. Heavy emphasis on science and engineering education in countries including China and India assures investors of a steady flow of new, local talent. Affordability and access to potential research subjects has fueled recent expansion of clinical trials outside the traditional US/Europe centers. Corporate mergers of large life science companies create multisite organizations overnight. The promise of personal medicine and nanotechnology often developed by small research-based firms, along with the shrinking pipelines of large life science companies, encourages corporate acquisitions. Supply chains routinely stretch across multiple national borders and include scores of suppliers. Surrounding these business and industry-specific factors are regulatory compliance responsibilities that affect every aspect of business, from the quality of a company's research to the integrity of its supply chain.

At the intersection of these issues is training that can drive consistent knowledge across the enterprise, target the knowledge needs of diverse and often fluctuating workforces, comply with exacting US and international regulatory requirements, ensure product quality and supplier performance, and support a strong culture that promotes compliance and ethical behavior.

- **Consistent Enterprise-Wide Knowledge.** Online learning enables distribution of the same content across the organization at the same time, ensuring that everyone is on the same page. Instructor-based training inevitably differs from place to place and day to day. It depends on the quality of the individual instructor. Logistically, it is impossible for the same instructor to provide training at multiple sites simultaneously. It is just as impossible for any single instructor to teach the same content in the same way over several days or weeks. Companies have recognized the importance of consistent knowledge – and the role online training plays in achieving that consistency.

- **Targeting Unique Knowledge Needs.** The best online training systems enable real-time management of student participation and training status. That oversight, in turn, allows managers to identify knowledge gaps, not only in individuals who may be unable to pass tests at the end of training sessions, but in specific facilities or even discrete job functions across multiple facilities. Based on that identification, managers can target remedial training to address knowledge gaps and restore consistent enterprise-wide knowledge.

- **Regulatory Compliance.** All products destined for sale in the US must comply with the FDA's quality, safety, training, and recordkeeping requirements including GxPs, SOP management, sales and marketing, and postmarket studies, regardless of the location, ownership, or management of the facility and its suppliers. FDA's GMP standards also serve as the basis for the regulations

of many other countries. Two points are worth noting. First, FDA is only one of the agencies with regulatory and enforcement authority over the life sciences industry. The US Department of Justice and the Securities and Exchange Commission enforce laws including the Foreign Corrupt Practices Act, the False Claims Act, and a broad spectrum of financial regulations. Second, global companies are regulated under the laws of different countries that may have extraterritorial reach. Various anti-corruption laws, including the UK's Anti-Bribery Law slated for implementation in 2011 and the FCPA, apply across a company's enterprise to subcontractors, agents, suppliers, subsidiaries, and strategic partners. In addition, government agencies including the Environmental Protection Agency, the Department of Transportation, the Occupational Safety and Hygiene Administration and state regulators impose regulations that will affect how a company operates and how it pursues training. Compliance requires documented training but the standard of effectiveness is that the training be understood and able to be applied by learners.

- **Product Quality.** Recent product recalls and the resulting anger among legislators, regulators, and consumers have triggered calls for increased facility inspections, heightened regulatory scrutiny, and more stringent enforcement of quality standards. Those calls remind brand companies that they are ultimately responsible for the quality of their products, no matter how many suppliers contribute to the finished product. Many brand companies have extended training to their suppliers and subcontractors as a means of managing the risks of product quality failures and regulatory noncompliance. Equally important from a supplier's perspective is the ability to demonstrate the same compliance standards and training as those of the brand company. Similarly, companies seeking to become suppliers are well advised to implement training systems that can integrate with standard technologies in use by the business community and that are consistent with the training implemented by the brand company.

- **Reinforcing Corporate Culture.** A network of dispersed facilities and operations intensifies the need for a strong, consistent corporate culture – and intensifies the difficulty in maintaining that culture enterprise-wide. Industry leaders have been especially forceful about implementing and continually reinforcing strong ethics training programs for employees, subcontractors and suppliers. The US Sentencing Guidelines confirm the role of organizational ethics in an effective compliance program. It is worth remembering that the measure of effective compliance is not that training is provided, but that it is understood and able to be applied by learners. Research demonstrates that ethics training in particular must be regularly reinforced through messaging, formal training, encouragement for reporting potential misconduct, and quick action responding to any reports.

Optimizing Business Operations

An organization's most valuable asset – or greatest risk – is its workforce. The value of a company's workforce to the organization's regulatory compliance, operational performance, and ultimate competitiveness in the global marketplace is defined by its knowledge and ability to apply that knowledge.

While employees shoulder responsibility for learning, regulators hold companies responsible for ensuring that their workers, whether full-time employees or temporary contractors, perform their jobs in compliance with regulatory requirements. At the same time, corporate officers and managers carry the responsibility for ensuring efficient, productive operations that deliver value for shareholders and investors.

Effective training has always been important for regulatory compliance and efficient operational performance. It has never been more essential than it is today. Business leaders recognize that occasional in-person training alone will not meet the knowledge needs of their organizations in 2011. Today's knowledge management programs must be about the professional development goals of employees as well as the training needs of organizations. Providing those programs across global organizations requires the use of creative online resources that target the needs of individuals, job functions, and corporate operations. In fact, the road to compliance, performance and staff development has moved to the virtual world, where it stretches across an organization and around the globe. ■

***Carrie McKeague, PhD**, serves as Chief Learning Officer at Kaplan EduNeering and has over 15 years of experience in the field of adult learning theory and instructional design. Readers can contact her at carrie.mckeague@kaplan.com*

Update on DIA's Digital Initiative

As we reported in the February issue of the *Global Forum*, DIA, has embarked on an exciting digital initiative. This initiative is an essential component of the 2011-2013 Strategic Plan, which the Board of Directors approved in December 2010. The first digital initiative milestone was the launch of DIA ConneX, the association's private social networking platform. Recently, we conducted a beta test of a mobile agenda app at the EuroMeeting, and we plan a further rollout of an agenda app at our upcoming DIA 2011 Annual Meeting in Chicago.

DIA is pleased to announce our recent beta test of mobile applications for use by attendees at our 23rd Annual EuroMeeting, held in Geneva, Switzerland, March 28-30. The EuroMeeting app served as a complement to the current web and print offerings and allowed attendees to stay apprised of the latest show information from their mobile devices. In the continuing effort of the EuroMeeting to grow "greener," these mobile apps helped to move the meeting further along toward paperless information sharing. The mobile apps take full advantage of the power of the web and mobile devices and enable the delivery of event information and an infrastructure that connects attendees, speakers, and exhibitors with each other.

Features of the EuroMeeting App

Interactive Scheduling & Automated Reminders
Attendees could review the conference program beforehand and choose the sessions they wished to attend, instantly adding it to their calendar as they built their agenda.

Event Announcements & Breaking News
Announcements and changes in the program were easily communicated to attendees.

Professional Networking
Attendees had the unique opportunity to network with other attendees and exhibitors in a virtual environment via their mobile phone. Email addresses were secured to avoid spam tactics. Attendees controlled the information they were comfortable making available to the show public.

Search
A powerful search function enabled participants to find speakers, topics, colleagues, and more.

These features truly gave attendees the ability to personalize and streamline their time at the EuroMeeting. Now that the EuroMeeting has wrapped up, DIA is gathering feedback from attendees who used the mobile apps and will use that information to create an app for the upcoming 47th Annual Meeting, DIA 2011. These two groups of apps help DIA meet the rapidly changing needs of our members, customers, and other stakeholders.

Digital Editions and Mobile Apps for *Global Forum and Drug Information Journal*

The digital editions of the *Drug Information Journal* and the *Global Forum* are exact replicas of the print editions, including the advertising. This allows readers to have the familiar experience of virtually thumbing through a print publication while being able to access the additional features of an online pub, including robust search feature and hyperlinks. Readers can search for topics in the issue, or click on links and be taken to external websites. They can also clip pages and save them, or even forward them to share ideas and information with colleagues.

The technology in DIA's digital publications is fully compatible with the browser that powers the iPhone and iPad. Readers can immediately access the digital editions, without needing a special add-on or plug-in.

Members with iPads and iPhones will be able to download the latest issues of the *Global Forum* and the *Drug Information Journal* beginning with this issue of the *Global Forum*. Once members have downloaded these free apps from Apple's App Store, they will simply log in with their email address to receive and read the current issues.

Successful Launch of DIA ConneX

DIA's professional networking tool, DIA ConneX, has been well received by SIACs and members, who have commented favorably on its ease of use, flexible collaboration tools, and robust set of discussion forums, file management, and search functionality. With DIA ConneX in place, SIACs can continue their focus on developing communities of practice globally.

Dr. David Clemow, Eli Lilly and Company, Medical Writing SIAC Co-Chair, commented "DIA ConneX allows for better connectivity amongst members with a focus on easy communication. It enables SIACs to organize and communicate at the regional level, while still being plugged into the global SIAC. The launch of DIA ConneX was an immediate improvement to prior solutions because it is easier to access the site, and easier to find the information you need quickly. "

DIA ConneX displays recent content on each SIAC's homepage along with other vital SIAC information, and its "Pulse" feature is dedicated to sharing the newest updates. Dr. Clemow noted that, "The ability to move seamlessly across different SIACs allows for better collaboration opportunities. Getting involved and joining SIACs is much improved and streamlined with the launch of DIA ConneX."

Carlos Fulcher, Worldwide Deputy Executive Director, DIA, summed up the response to the launch of DIA Connex in this way, "DIA ConneX will enable all our stakeholders to collaborate and communicate across regions, taking advantage of DIA's value as a neutral forum for problem solving."

DIA continues to work on simultaneous projects to better leverage the association's position in a digital environment. These projects include a new website content management system and taxonomy, as well as a new website design. Please continue to monitor the *Global Forum* for further updates on our progress. ■

Clinical Trial Gives Autistic Patient with SEGAs His "First Win"

When Debora Moritz enrolled her 10-year-old son, Griffin, in a clinical trial at Cincinnati Children's Hospital Medical Center in October 2008, the stakes couldn't have been higher.

Griffin, who is autistic and nonverbal, suffers from tuberous sclerosis complex (TSC), a rare genetic disease that causes noncancerous tumors to grow throughout the body. Griffin had long suffered from frequent and severe seizures and from facial and kidney tumors. Recently he had developed subependymal giant cell astrocytomas, or SEGAs, deep in the ventricles of his brain. The SEGAs were causing hydrocephalus or fluid on the brain. Unless the pressure on his brain was alleviated, Griffin would die.

At the time, surgery was the standard treatment for SEGAs. Unfortunately, because of the location and nature of his tumors, Griffin wasn't considered a promising candidate. Surgery might help, but it wouldn't eliminate all the SEGAs. The Cincinnati trial was testing the effect of everolimus, a Novartis drug used to treat advanced kidney cancer, as an alternative means of treating SEGAs.

Griffin's neurologist sent the boy's films to Cincinnti Children's for evaluation. The research team called the next day. Griffin was a perfect candidate for the phase 2 trial. In October 2008 Griffin enrolled as the twenty-fifth participant in what researchers estimated would be a 25-participant trial.

For Debora, deciding whether to join the trial was a daunting process. It wasn't the informed consent process she found intimidating. As Griffin's advocate, she's accustomed to the language of doctors. Through the Tuberous Sclerosis Alliance she keeps up on the latest research and attends medical conferences when possible. Griffin's condition is so complex she's participated in conference calls with her son's endocrinologist, nephrologist, neurologist, and pediatrician, "trying to figure out 'who's on first' with an issue."

The protocols weren't a sticking point either. "It wasn't what was required to participate in the trial that concerned me. The baseline for participation was all stuff we'd been through before. Blood draws? We'd done that a million times. MRI? We knew he needed to be fully anesthetized for that. Twenty-four hour video EEG? We knew the drill there. The components of the trial—other than the medicine—were all things that had been part of our life before."

Rather, she says, it was the potential consequences of her decision that kept her up at night.

"I kept second-guessing myself," she recalls. What was hard was this trial drug had a potential side effect of immune suppression," she recalls. If the trial drug didn't work and Griffin's immune system was suppressed, he might have to wait even longer to undergo brain surgery to alleviate the hydrocephalus. In the end, Debora says, "We rolled the dice."

Journey Toward Hope

After enrolling in the study and completing his initial clinic visit, Griffin returned to Scottsdale with Debora. The trial requirements weren't onerous: take a daily pill, complete a quality-of-life survey and have periodic blood draws and MRIs. But traveling cross-country with an autistic, seizure-prone child for routine follow-up visits was challenging, Debora recalls. Even though their travel expenses were largely paid for by the trial, and the research staff always made sure their accommodations were comfortable and they had transportation to and from the airport, there were obstacles.

"Once we got diverted to Louisiana because of storms, and another time we flew into the worst snow storm Cincinnati had ever had," she says.

At the six-week mark, Debora and Griffin returned to Cincinnati for blood work, and his dosage was increased. They made the trip again at 11 weeks. During the course of the trial, Griffin experienced only minor side effects: mouth ulcers and a slight elevation in his cholesterol. But Debora says early in the trial she began observing positive, unexpected side effects as well.

"I'd created a chart so I could be objective in recording any changes," she says. "I started noticing differences within the first week. His face where he had bumpy red tumors (angiofibromas) looked less red and then less bumpy. You could see week by week that his face was looking clearer, and I was noticing changes in his behavior. I was seeing interaction differences, and he was calmer. But I couldn't see inside his head."

A Look Inside

In February 2009, Griffin and Debora flew to Cincinnati for his 15-week clinic appointment. She would finally have her chance to see inside his head. Although the trip was a nightmare—they flew in during a blizzard and Griffin wasn't allowed to eat because he would receive anesthesia the following day—the MRI moved forward as planned.

"He got the MRI at 10 AM and by 11 AM they were looking at his pictures on the monitor," Debora recalls. "I walked in and one of the doctors turned to me with a big thumbs-up. I'm a lay person. But looking at that MRI, even I could see the ventricles were more normal." Griffin's SEGAs had shrunk by 30 percent.

"It was his first win," Debora says, her voice catching with emotion. "Griffin has had a track record of getting the short straw on all the TSC manifestations. This kid never got a break: face tumors, kidney tumors, autism, infantile spasms, SEGAs. He was finally getting a win. That was a good trip—and he got to see snow."

Griffin's dosage was again increased. Debora and Griffin returned to Cincinnati in April 2009 at the six-month mark for another MRI, a video EEG, blood work and a neuropsychological exam. Between clinic visits, Griffin was allowed to have his blood drawn in Scottsdale, and Debora participated in telephone interviews with researchers. Throughout the trial, Griffin and other participants continued to show improvement.

Results were so impressive that in October 2010, the US Food and Drug Administration granted accelerated approval of everolimus, which is marketed under the tradename Afinitor®, for patients with SEGAs associated with tuberous sclerosis. Study results were published in *The New England Journal of Medicine.*

More than three quarters of the 28 patients who participated in the Cincinnati Children's study experienced a 30 percent or greater reduction in their SEGAs by six months. In addition, patients with active epilepsy had an 86 percent reduction in seizure frequency. Every patient in the study experienced a decrease in tumor size, and none required surgery after treatment. The everolimus not only resolved hydrocephalus, it improved malformations of the brain tissue itself.

The Road Ahead

Today, Griffin's SEGAs are 60 percent smaller than when he entered the trial and he's experienced numerous other benefits. On January 11, 2010 he celebrated a milestone: 30 days without a seizure. For a child who used to suffer as many as a half dozen serious seizures a day, "it's been unbelievable," says Debora. The lesions on his face have largely cleared, the tumors in his kidneys have stopped growing, and Griffin has become more independent.

Now 13, Griffin can eat with a spoon and fork and communicate with modified sign and an augmentative communication device, Debora says. He listens better, responds faster, has a longer attention span and is learning better in school.

Meanwhile, researchers continue to explore everolimus' potential. Griffin is involved in an extension study of everolimus at Cincinnati Children's to evaluate the drug's tolerability and long-term impact on SEGAs.

And Debora? Like many mothers, she's posted her kid's picture on Facebook. The only difference: the pictures are "before" and "after" MRIs of Griffin's brain. "I tell people, 'This is my kid's brain' and 'This is my kid's brain on drugs,'" she says happily. It's her way of promoting clinical research. ■

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."

Career Opportunities in Clinical Drug Research

By Rebecca J. Anderson

Reviewed by Betty R. Kuhnert

Rebecca J. Anderson: Career Opportunities in Clinical Drug Research
Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. Copyright © 2010, Cold Spring Harbor Laboratory Press.

You can't find a job because you don't have the right experience, and you can't get the right experience because you don't have a job. This is often the dilemma for entry-level job seekers in the pharmaceutical industry. The job search may be made more difficult because recent graduates often aren't even aware of the myriad of job opportunities available, particularly in clinical research. The book by Rebecca Anderson addresses these issues and is an excellent resource for job seekers. But it would also be helpful for recent hires new to the industry, as well as for more experienced staff who mentor less-experienced colleagues.

A better title for the book might have been, "Everything You Wanted to Know about the Pharmaceutical Industry, But Were Afraid to Ask," or "The Pharmaceutical Industry for Dummies," because it goes well beyond career opportunities. The book also has a reasonable glossary, an acronym list, and an extensive list of reference materials including websites, professional organizations, and lists of top companies. For example, if you had forgotten what "CDISC" stands for, or the difference between safety and pharmacovigilance, you can easily find it. The first part of the book provides a brief introduction to clinical research, to drug and device development, and to what happens at a clinical site. This information sets the stage for the discussion of "career opportunities" in part two of the book.

The second part focuses on what people in entry-level clinical operations jobs do, what qualities they need and how to get "clinically relevant" experience to qualify for these jobs. Individual chapters describe the various opportunities in clinical operations (or related departments) including monitoring, data management, biostatistics, QA, safety, and medical writing. A final chapter on opportunities for career development describes higher level positions such as project, clinical study, clinical standards, and clinical training managers. This information would be very helpful for recent hires who may be participating in team meetings with only a vague idea of what the person from another department sitting next to them actually does.

The third part of the book provides specific advice for job seekers. It offers pearls of wisdom for today's candidates such as, "If you have tattoos, wear clothing that covers them for the interview," and, "Avoid using text language in written correspondence," as well as advice on what should not be on social networking sites. It also includes helpful sample interview questions and hints on how to network. This section is well done and reflects the author's long experience as a hiring manager.

The book is written in a simple fashion, perhaps too simple, with each of the members of the clinical team given names (eg, "Mike" the medical writer) and working for a fictional company called CanDo Pharma. Each of the chapters describing the clinical operations team members is structured in the same way. The positions, the person's role, and how they interact with the rest of the clinical operations team is described. Each chapter has a section on "One of Mike's Days," a

section on how "Mike" got his job; finding a position in his department; landing the job; opportunities for career development; and resources. Because the chapters follow a formula, there is considerable redundancy in the text for someone reading the whole book, ie, each chapter has a sentence that says, "All of the hiring managers ranked 'Mike' as a highly desirable candidate." Then it explains why he was a desirable candidate for that discipline. Each chapter also has many other redundancies, such as the same sentence stating that staff should join professional organizations.

There are also some misstatements and a lot of questionable generalities: For example, "Phase 3 studies are called pivotal studies"; and "Most of the opportunities for clinical research jobs are in the US." A lot of pharmaceutical professionals, particularly those in data management, might not agree with the latter statement. Generalities include: "Clinical departments are generally very pleasant places to work," and "Everyone is bright, hardworking, considerate and talented." These statements must refer specifically to the ideal world at CanDo Pharma.

The author did a better job being realistic about the day-to-day frustrations and conflicts in the chapter on "Mike," the medical writer, than in many of the other chapters. She states that one of the characteristics hiring managers look for in medical writers is being able to keep cool under pressure and another is to meet tight deadlines. In the section on "Mike's" day, the author states that, "Mike knows that CanDo Pharma's executives are easily distracted by more interesting activities, and reports languish unsigned for a long time unless Mike sends gentle reminders." Also, "Mike's progress on the diet study report has already been delayed a number of times by higher priority tasks," and finally, "Sometimes Mike must referee conflicting written comments." Perhaps this more realistic portrayal is possible because the author herself is currently a freelance writer.

Those of us who have spent many years in the pharmaceutical industry may laugh at statements such as "Everyone is bright, hardworking, considerate and talented," and terminology such as "languishing reports" and "gentle reminders." However, those new to the industry and those trying to break in to the industry will find this book very helpful, if not completely realistic. ■

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Featured Jobs Articles Coming Soon to the *Global Forum*

Are you looking to change jobs?
Have you ever wondered what your colleagues do?

In the near future, the *Global Forum* will begin offering an articles describing specific jobs within the pharmaceutical and life sciences industry. We invite readers to submit articles describing such jobs, including education/experience, qualifications, responsibilities, where the job fits into the drug development (or other) spectrum, opportunities for employment, advancement, etc.

Betty Kuhnert will serve as the section editor/coordinator for these articles.
Please submit your articles to Fran Klass at Fran.Klass@diahome.org.

Regulatory Updates: Harmonization

To update members about regulatory activity around the world, DIA provides a weekly **DIA Global Regulatory Activity Digest** for members who opt in to receive it. DIA has licensed this content from Thomson Reuters, parent of the IDRAC regulatory database; to access the actual documents summarized therein, you must become a subscribing IDRAC member on their website.

Recent regulatory updates on the topic of harmonization, the special focus of this issue, plus updates of topics associated with the International Council on Harmonization, include:

Brazil - ANVISA Information Note: Regulatory Agenda for 2011, 18-Feb-2011
ANVISA made public the agenda for 2011 of the subjects that will be discussed in the course of the year and which require most of the attention. The agenda covers 93 subjects, among which ANVISA is going to assess the effective regulation on Good Manufacturing Practices and the harmonization of marketing authorization regulation. The Brazilian health agency will also discuss subjects on Good Manufacturing Practices of excipients.

European Union: Implementation Information for the New eCTD & NeeS Validation Criteria 2011, 28-Jan-2011
This document provides information on the newly published validation criteria for eCTD and NeeS, proposed by the TIGEs Harmonisation Group. It is important to note that the new validation criteria will apply from 01-Sep-2011 and will be used for the validation of all electronic submissions received from 01-Sep-2011 to the National Competent Authorities and the European Medicines Agency.

European Union - EMA/676305/2010: Work Plan for the Biostatistics Working Party, 27-Dec-2010
This document provides the work plan for 2011 for the Biostatistics Working Party. It covers the following topics: - Meetings scheduled for 2011 - CHMP guidelines and related documents - CHMP/ICH guidelines and activities - EU regulatory activities - Activities with external parties.

European Union - EMA/CHMP/PGxWP/250429/2010: Work Plan for the Pharmacogenomics Working Party, 22-Dec-2010
This document provides the work plan for 2011 for the Pharmacogenomics Working Party. It covers the following topics: - Meetings scheduled for 2011 - Product-related issues - Reflection papers and guidelines - ICH activities - EU regulatory activities - Activites with external parties/stakeholders - Organizational matters.

European Union - EMA/INS/GMP/79818/2011: Note for Guidance on Pharmaceutical Quality System (ICH Q10), 31-Jan-2011
This guideline provides information on the quality management system, which is based on the quality ideas of the International Standards Organisation. The guidance offered here can be implemented throughout the different stages of a medicinal product life cycle. Consequently, it goes beyond the current GMP requirements which do not pertain to the development part of the life cycle (excluding the manufacture of investigational medicinal products for human use). At the time of EU implementation of ICH Q10 (in 2008) Chapters 1 (80163), 2 (16503) and 7 (16521) of the GMP guide were considered to need updating so as to be in line with the terms and ideas present in ICH Q10. The aim of this guideline is to make the innovation and continual improvement of medicinal products easier, in addition to making the connection between the pharmaceutical development and manufacturing activities stronger. This guideline also complements ICH Q8 (95297) and ICH Q9 (55386). This document applies to the systems which support the development and manufacture of pharmaceutical drug substances and drug products throughout the life cycle of the medicinal product. It should be noted that most of the content of this guidance document is currently specified by regional GMP requirements and therefore the content of this guideline that is additional to the GMP scope is indeed optional.

European Union - EMA/INS/GMP/79766/2011: Quality Risk Management (ICH Q9), 31-Jan-2011

This Guideline provides information on the quality risk management. It explains more specifically the principles and some of the tools of quality risk managment that can enable more effective and consistent risk-based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products accross the product life cycle. It contains two Annexes: Annex I: risk management methods and tools and Annex II: potential applications for quality risk management.

International - ICH Guideline Topic Q3C (R5) Step 4: Impurities: Guideline for Residual Solvents, 04-Feb-2011
This Guideline has been revised to integrate the PDE for Cumene document (as part IV), approved by the Steering Committee under Step 4 and recommended for adoption to the three ICH regulatory bodies. This document includes an update of Table 2, Table 3, and Appendix 1 to reflect the revision of the PDE for Cumene. This guideline is divided in four parts: Part I: Impurities: Core Guideline: Guideline for Residual Solvents (coded as Topic Q3C, Step 4, 17-Jul-1997); Parts II and III: Impurities: Residual Solvents (Maintenance) (coded as ICH Guideline Topic Q3C(M), Step 4: Maintenance of ICH Guideline on Impurities: Residual Solvents - Permissible Daily Exposure (PDE) for Tetrahydrofuran (THF) and N-Methylpyrrolidone (NMP), 12-Sep-2002 (Version Corrected 28-Oct-2002); Part IV: Impurities: Residual Solvents (Maintenance) (coded as PDE for Cumene). Conclusion: According to the newly calculated PDE for cumene, it is recommended that cumene should be placed into Class 2 in Table 2 in the ICH Impurities: Residual Solvents Guideline (Q3C).

Japan - PFSB/ELD Notification No. 0127/1: ICH Guideline Topic Q4B Annex 10(R1) Step 4: Evaluation & Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Polyacrylamide Gel Electrophoresis General Chapter, 27-Jan-2011 (Japanese version)
This annex is the result of the Q4B process for Polyacrylamide Gel Electrophoresis General Chapter. The official pharmacopoeial texts, the Section in Ph.Eur. 2.2.31. Electrophoresis entitled Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE), JP General Information 23. SDS-Polyacrylamide Gel Electrophoresis, and USP <1056> Biotechnology-derived Articles – Polyacrylamide Gel Electrophoresis, can be used as interchangeable in the ICH regions.

Japan - PFSB/ELD Notification No. 0127/2: ICH Guideline Topic Q4B Annex 9(R1) Step 4: Evaluation & Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Tablet Friability General Chapter, 27-Jan-2011 (Japanese version)
This annex is the result of the Q4B process for Tablet Friability General Chapter. The analytical procedures described in the official pharmacopoeial texts, Ph.Eur. 2.9.7. Friability of Uncoated Tablets, JP General Information 26. Tablet Friability Test, and USP <1216> Tablet Friability, can be used as interchangeable in the ICH regions.

Japan - PFSB/ELD Notification No. 0127/3: ICH Guideline Topic Q4B Annex 11 Step 4: Evaluation & Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Capillary Electrophoresis General Chapter, 27-Jan-2011 (Japanese version)
This annex is the result of the Q4B process for the Capillary Electrophoresis General Chapter. The analytical procedures described in the official pharmacopoeial texts, Ph.Eur. 2.2.47. Capillary Electrophoresis, JP General Information 4. Capillary Electrophoresis, and USP General Information Chapter <1053> Biotechnology-derived Articles – Capillary Electrophoresis,1 can be used as interchangeable in the ICH regions.

Japan - PFSB/ELD Notification No. 0127/4: ICH Guideline Topic Q4B Annex 12 Step 4: Evaluation & Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Analytical Sieving General Chapter, 27-Jan-2011 (Japanese version)
This annex is the result of the Q4B process for the Analytical Sieving General Chapter. The analytical procedures described in the official pharmacopoeial texts, Ph.Eur. 2.9.38. Particle-size Distribution Estimation by Analytical Sieving, JP 3.04 Particle Size Determination entitled Method 2. Analytical Sieving Method, and USP General Chapter <786> Particle Size Distribution Estimation by Analytical Sieving, can be used as interchangeable in the ICH regions.

Japan - PFSB/ELD Notification No. 0221/1: ICH Guideline (Topic Q3C(M), Step 4): Revision of Guideline for Residual Solvents, 21-Feb-2011 (Japanese version)
This document presents the amendments of ICH Guideline, Topic Q3C(M), Step 4: Guideline for Residual Solvents. Revised PDE for Cumene has reached Step 4 of the ICH process and was integrated. The original English text of PDE for Cumene is available: Part IV of ICH Guideline Topic Q3C (R5) Step 4: Impurities: Guideline for Residual Solvents, 04-Feb-2011 (120098).

USA - MAPP: Chapter 5016.1: Applying ICH Q8(R2), Q9 & Q10 Principles to CMC Review, 08-Feb-2011
This MAPP outlines and clarifies how the chemistry, manufacturing, and controls (CMC) reviewers in the Office of Pharmaceutical Science (OPS) should apply the recommendations in the ICH Q8(R2), Q9, and Q10 guidances to industry. Because of an increase in the number of NDAs, INDs, ANDAs and BLAs containing QbD approaches, the Center recognizes the need for reviewers to consistently implement the ICH guidances in their reviews.

To learn more about IDRAC, please visit http://thomsonreuters.com/products_services/science/science_products/a-z/idrac/ ■

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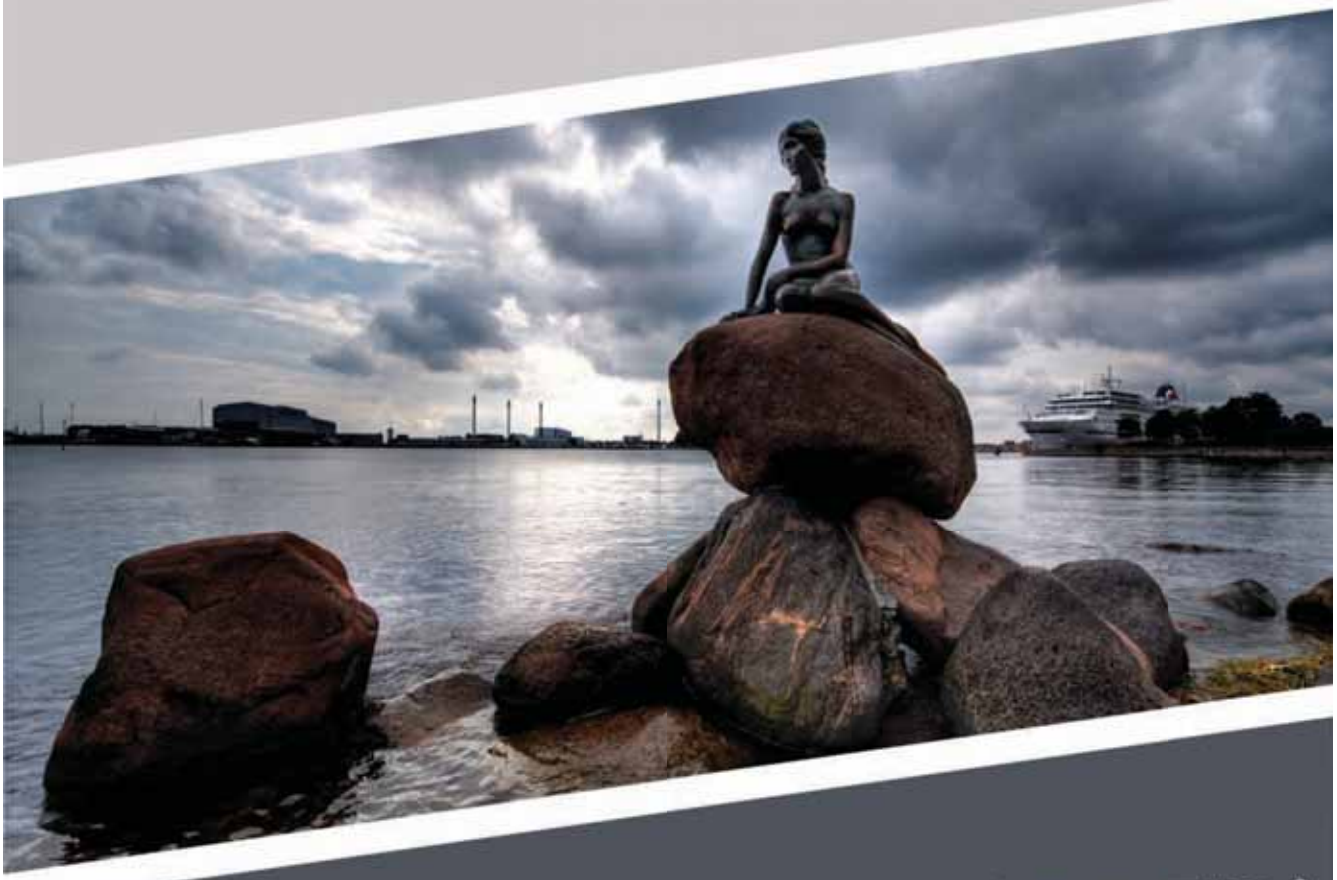

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