ARIS GLOBAL understands that by reducing the cost and complexity of safety, you can focus on what you do best.

agOnDemand™ eliminates the need to invest in new hardware, software or support staff by giving you a ready-to-use solution on a subscription basis.

Fast deployment—typically in a matter of a few weeks—lets you easily ensure compliance and manage risk. 24x7 availability and end-to-end support give you total peace of mind.

A growing list of life science companies and CROs, from small to large, have chosen agOnDemand.

Request the agOnDemand white paper.

Visit www.arisglobal.com/WP_agOD
Not too many of us remember the early days of CIOMS activities in drug safety which formed the basis for a series of truly groundbreaking ICH documents. With time, they became part of the legal framework in many countries worldwide. The cooperation, brainstorming, and discussions between regulators and industry brought about a major change in understanding and delivering safety information in the pharmaceutical sector and regulatory environment with substantial emphasis on content and quality. The CIOMS I-V documents compiled from the mid 1980s through the end of the 1990s, as well as the ones from the last decade, were based on the best knowledge accumulated among regulators, industry scientists, and academics.

At present, a growing number of voices from the external environment perceive any interactions between regulators and industry as a threat to public health, quality of drugs, and the independence of decision making. Despite that, those more closely involved in such cooperation, who possess a better understanding of the complexities and science in the field, would disagree with this perception. It must be said that the historical records of such cooperation and its achievements support their position. There is substantial knowledge and expertise on all sides of the “table,” and the ability to discuss concepts and ways to solve problems and move forward facilitates more rapid and fruitful progress. An informed observer would understand...
that the majority of innovations in pharmaceuticals (as in other forms of business) are created by industry. As a result, scientists from academia or the regulatory world can only learn about such innovations first hand from this source. There are numerous examples of this over the years, such as biotechnology drugs.

In our April 2011 issue, we celebrated 20 years since the beginning of the ICH process, which has proven to be a very successful cooperation between scientists across the world. The current issue focuses on drug safety/pharmacovigilance, returning one and a half years later to a topic similar to that covered by the Risk Management issue in February 2010. The articles show how much the approach to safety matters has changed since the first formal worldwide documents created by CIOMS in the 1980s and since the first widely known risk management program was implemented (clozapine, 1989). Individuals from industry, academia, and the regulatory arena have worked very hard over the past 25 years (CIOMS I – 1986) to address vital aspects of submitting, analyzing, and presenting data to assess benefits and risks for patients, and to provide the best products in the safest possible way. Our special section this month presents some of these aspects.

Many years ago, in my regulatory days, I tried to organize the best ways of exchanging information and knowledge across different environments/groups, and this is certainly one of the reasons why I became a member of DIA. On many occasions, I also brought up the concept of a form of sabbatical for regulators to temporarily work in the industry so that they could better understand the regulated side of the coin. A substantial number of regulators moved to the industry, bringing their regulatory knowledge with them. However, the reverse situation of industry employees moving to the regulatory world is very rare. Therefore, a method that would accomplish this knowledge transfer to the regulatory area would be very helpful in this complex environment. I feel even more strongly about it now since, once I made the move to the industry, I realized how right the concept was, since the regulatory perception of most industry business and matters as seen from outside is built rather on best imagination (as it was in my case in those days), than on facts, knowledge, and reality.

As mentioned above, nowadays we experience a growing pressure to build even greater “walls” between these two environments. This view finds many supporters, despite the fact that such a division is against the “open world” environment for science, and creates hurdles for development, accessibility of new medicines, and practices in assessing benefit risk of innovative drugs. Large projects such as IMI (Innovative Medicines Initiative) have proven that cooperation can be very successful on scientific grounds. All voices raised against collaboration of the two environments should reconsider their views, look at historical records, and move forward in support of cooperation, instead of standing against it.

It is, therefore, desirable for all those involved in “across the table” cooperation over the past 30 years to raise their voices in support of continuing it for the benefit of the future in terms of new treatments, health care, and public health. While I remain hopeful that this will happen, in the meantime I would like to thank Steve Jolley for having such successful oversight in the series of articles on pharmacovigilance in this issue. I also encourage our readers to read all the other articles in this issue, including the profile of Dr. Dolores Montero who, during the Spanish Presidency of the EU, led the new Pharmacovigilance law to achieve final approval.
DIA’s Board of Directors has devoted much of its time and energy toward advancing our Association’s global world view. I am pleased to say that, for many reasons, this vision is now becoming a reality.

As the first European President of the Board of Directors, I have long been involved in international activities like the ICH Steering Committee. I’m delighted to serve DIA, an Association that truly understands the importance of responding to the global challenges we face as professionals. My presidency, together with the composition of our Board of Directors, regional advisory councils of North America, Europe, Japan, India, China, and most recently our provisional Advisory Council of Latin America, supports our Association’s claim that all members, wherever located, can play a key role in helping to shape the future of both DIA and the health care industry.

**Going Global**

International harmonization is driving the game. All of us live and work in a world that is decidedly more global, but we do so in specific locations, often with specialized needs. One of my goals as DIA president is to lead our Association’s efforts to meet the professional needs of our members and customers, both regionally and globally. The current state of global harmonization requires that DIA continues to provide knowledge, information, education, and training to professionals around the world — regardless of their location, professional level, or job function.

The DIA 2011 Annual Meeting, which was held in Chicago this past June, represented a real step forward in this process. Even if a majority of participants very naturally came from the US, the program was able to meet the educational and professional needs of attendees from 80 countries. There were interactive Town Hall Meetings presented by the European Medicines Agency, the European Heads of Medicines Agencies, the India Regulatory Agency, and representatives of regulatory agencies from all around the world. We were very pleased to welcome more than two hundred attendees to our DIA Japan annual meeting luncheon. The Gates Foundation also presented a session on vaccine development for low-income economic regions around the world.

DIA is also in the process of creating a Global Training Plan that matches the local needs in each region. There is great need for training in Asia and in Latin America, for example, and we have to work in partnership with local and regional health authorities, as well as with the ICH Global Cooperation Group to help meet this need.

Similarly, we will continue to hold international educational programs and to work in partnership with like-minded organizations. This past April, for example, DIA co-sponsored the Asia-Pacific region’s first Asia Regulatory Conference, in Seoul, with the Asia-Pacific Economic Cooperation (APEC) Harmonization Center (AHC) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).

Another prime example of DIA’s global collaborative reach is our upcoming Conference on the Quality of API, scheduled for September in Mumbai, India, which we will present in collaboration with the World Health Organization (WHO) and the European Directorate for the Quality of Medicine & Healthcare (EDQM), the European Pharmacopoeia.

Our European office’s initiatives include the involvement of people working in academics, illustrated by our upcoming Paediatric Forum in London in September, which DIA will present in
partnership with the EMA and European Forum for Good Clinical Practice (EFGCP).

Developing Safe and Effective Products
The aim of all DIA members and stakeholders is to contribute to the provision of pharmaceutical products that are as effective and safe as possible. Despite all the real progress that has been made, pharmacovigilance is still a very hot and complex topic. For example, we know that signal detection might not be enough in several cases to reveal long-term side effects. This is something that we really have to work on, specifically in two aspects: First, we need specific pharmacoepidemiology studies to compare the level of risk for patient populations who are using a specific drug versus the same populations who are not.

Second, we have to try to minimize or mitigate the risk by developing some specific preventive actions within the framework of the risk management plan. This second aspect needs to be developed in cooperation with all stakeholders, including, of course, regulatory and health authorities, health professionals, physicians and pharmacists, the pharmaceutical industry, but also patient groups.

I have seen the emergence of this activity, and I am very interested to see the development of the two main aspects of pharmacovigilance: safety in clinical trials and post-marketing. That’s where DIA is really able to bring people together to share best practices and discuss the latest developments in those areas. DIA has been and will continue to be, very proactive in the area of risk management, specifically in emerging countries where side effects can be the first signal of low quality or even counterfeiting.

Throughout my career, I have always worked to bring people together to find proactive and consensual solutions to the challenges they face. As Board President, I can ensure that DIA will continue to promote the sharing of ideas, integrate different viewpoints, and recognize and acknowledge diverse insights and contributions. Ultimately, this is what DIA is all about.

pm1-presidents.message.indd   4
7/26/11   7:13 PM
Stand out from the crowd.

If you’re in regulatory, there is one clear way to distinguish yourself in the world of healthcare products.

And that is earning Regulatory Affairs Certification (RAC). It’s the most meaningful designation in the profession. Having “RAC” after your name shows you’ve completed the rigorous study and preparation necessary, and passed the RAC exam. And that’s a good thing.

Autumn 2011 registration deadline: 8 September
6

OPEN FORUM
1  Importance of Open Cooperation
   Andrzej Czarnecki

PRESIDENT’S MESSAGE
3  Global Vision Becomes Worldwide Reality
   Yves Juillet

EXECUTIVE DIRECTOR’S MESSAGE
8  Advancing Patient Safety
   Paul Pomerantz

BEST PRACTICES
10 Efficient and Cost-effective Site Monitoring During Observational Studies
    Ronald E. Weishaar

13 Clinical Trials in Emerging Latin American Countries
    Karen Politis Virk

17 Achieving Regulatory Information Management
    Gillian King

SPECIAL SECTION: PHARMACOVIGILANCE
20 Pharmacovigilance in 2011
    Steve Jolley, Section Editor

21 Managing Potential Safety Signals Detected through Quantitative Methods
    Robbert P. Van Manen

27 Integrating Signal Detection in the Pharmacovigilance System
    Giovanni Furlan

Mission
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.

Publishing, Subscription, and Advertising Offices:
Drug Information Association (DIA), 800 Enterprise Road Suite 200, Horsham, PA 19044-3595, USA.

Contact Information
Worldwide Advertising Sales, Michael Boucher 267 419 8735
Subscription Information, Customer Service 215 442 6100
Membership Services, Mike McGovern 215 442 6129
Senior Marketing Manager, Mike Keller 215 442 6173


The Global Forum (ISSN: 1944-1991) is published six times a year, in February, April, June, August, October, and December. Periodical postage paid at Horsham, Pennsylvania, and additional mailing offices. Thirteen dollars of each member’s annual membership fee is for a year’s subscription. Prices include postage and are subject to change without notice. Notify DIA eight weeks in advance of address change with a copy of the mailing label. Back issues of most previously published issues are available from DIA.

PUBLICATIONS MAIL AGREEMENT NO. 41103506
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO CIRCULATION DEPARTMENT, PO BOX 1051, FORT ERIE, ONTARIO L2A 6C7

Postmaster: Send changes of address to Global Forum, 800 Enterprise Road, Suite 200, Horsham, PA 19044-3595, USA.

Cover Illustration: Copyright © iStockphoto.com

DIA is a neutral organization that does not advocate for or against any issue. The views expressed by the individual authors or interviewees in the Global Forum are theirs and do not necessarily represent the views of the Drug Information Association.
30 Strategies to Uncover Troublesome Embedded Adverse Events
Carole DeRoche

33 The Importance of Proper Training in Terminologies for Quality Coding and Its Impact on Data Analysis
Samina Qureshi

37 The Developmental Safety Update Report
Giovanni Furlan and Steve Douglas

43 Effectiveness of REMS Tools
Sally Van Doren and James Buchanan

PROFILE
50 Dr. Dolores Montero

REGIONAL REPORTS
NORTH AMERICA
53 DIA 2011 Opening Plenary
55 Student Poster Awards
56 Images from DIA 2011

EUROPE
58 On Location: Basel
64 Following DIA Path from Student to Professional

CHINA
66 Scoring on the Chinese New Drug R&D Ability Forum

INDIA
68 Selecting a Vendor for a Central Lab
Deepti Sanghavi

JAPAN
72 5th Annual Conference in Japan for Asian New Drug Development
Hironobu Saito
73 PMDA & DIA Executives Address Luncheon

LATIN AMERICA
74 Harmonization of Latin American Clinical Trials Regulations Addressed

CAREER TIPS
75 Make Change Happen

PROGRAM NOTES
79 Assessing CV Safety in Drug Development

ASSOCIATION NEWS
48 Upcoming Events
81 DIA Announces 2011-12 Board of Directors
83 Patient Fellows’ Reflections on DIA 2011
84 DIA Expands Its eLearning Program
86 DIA Honors Retirees
87 Thomas W. Teal Remembered

REGULATORY UPDATES
88 New FDA IND Regulations: Consequences for our drug safety practices
Mariette Boerstoel-Streefland
91 Regulatory Updates: Pharmacovigilance and Safety

PATIENT PERSPECTIVE
93 Weighing the Risks of a New Implanted Device

95 MEMBERS ON THE MOVE
96 MARKETPLACE
Advancing Patient Safety

In considering this issue’s special focus on safety and pharmacovigilance, I reflected on the many instances in our daily lives when we take safety for granted; but this is sometimes not the case with pharmaceuticals and medical products. Take, for example, the complexity of airplane travel and how we take to the air with complete assurance that we will reach our destination quickly and safely. Why? Because we’re confident that the system works. And yet, at one time, the commercial air travel system did not work. With the dawning of the jet age, in the 1950s, there was much we did not understand about flight. Accidents were common, but these became learning experiences. The airline industry, government agencies, and consumer groups—all working together—developed the current systems and processes that assure our safety. This safety is the result of complex equations that involve science, technology, people, information systems, and equipment. But, we as passengers simply walk onto a plane, listen to some instructions, then sit back and travel to our destination. The key to this transformation has been transparency. An airline accident is a big event. All stakeholders are aware. The public demands answers and accountability. The system promotes rapid investigation. What we learn from these incidents is then translated into action, including new standards, regulations, training and/or equipment changes. This is a global system, where volunteer organizations such as the International Air Transport Association (IATA) and governments collaborate.

We’re currently in a time when there is a lot of public skepticism about the pharmaceutical industry, its practices, and the quality and safety of medical products. While we continue to learn new and better ways to manage and assure the safety of something so essential to our own well-being, the science of safety is still relatively new. We are regularly confronted by the fact that health care products can be very helpful, but also potentially harmful. This past May, for example, the FDA mandated that all producers of “metal-on-metal” artificial (replacement) hips conduct postmarketing studies to collect information, specifically blood samples, from patients who have received these devices, to determine the levels of metallic ions in their systems. Yet, there are presently no global requirements or systems in place to track, understand, and monitor these products. Monitoring the safety of these devices is critical. Safety cannot be an afterthought; it must be planned for upfront and managed throughout our processes. The articles in this special section point to several aspects of a successful approach to safety.

First, the assurance of safety requires a multidisciplinary approach among numerous stakeholders, including actively engaging both clinicians and patients in the process. This will require proactive strategies for outreach and training to these communities. A July 5 New York Times editorial addressed the issue of including plain language and real-world experiences with drug label and packaging information. Direct language would explain what a particular drug has been shown to do, its potential hazards, how many times those hazards have actually transpired, how effective it has been compared to similar products or a placebo, and other related information. Then, a patient, their physician and/or pharmacist can have a fact-based discussion about whether or not to take this medication.

Second, new advances in the electronic medical record, information technology and statistical analysis will provide opportunities...
to leverage real-world outcomes. Sophisticated statistical systems, for example, identify safety signals from large pools of complex data using computer analysis and other information technology.

Third, our approach to safety must be global to be truly effective. This requires more than just establishing harmonized safety standards (which are essential), but also the sharing of information and experiences among all stakeholders so that we can respond quickly when issues emerge.

Industry, regulatory, and consumer leadership have begun to recognize the importance of assuring the safety of the supply chain for these products. But, our processes must also secure a safe supply chain of reliable data. The right expertise must be available when data is handed off and communicated from one responsible party to the next, so that all parties involved know what they’re looking for and what to do once they’ve found it.

Building and maintaining trust in this system and confidence that all stakeholders are meeting these responsibilities may never be more important—or challenging—than it is today.

DIA assists in tangible ways: our training programs, workshops, conferences, and publications help stakeholders improve the execution of their responsibilities. Safety and pharmacovigilance have been longstanding components of our training curricula. Our Clinical Safety & Pharmacovigilance Special Interest Area Community (SIAC) is global and among our most active member/volunteer subgroups, and contributes the annual safety and pharmacovigilance workshop to our educational portfolio. This SIAC is co-chaired by Steve Jolley, who we thank for serving as section editor for the pharmacovigilance articles in this issue.

Looking back to our recent DIA 2011 Annual Meeting, our HIMSS Interoperability ShowcaseSM, a joint effort of HIMSS, DIA, CDISC, and IHE, demonstrated how the industry and regulatory sectors can work more efficiently, through information technology, with databases that capture, analyze, and report these experiences.

Finally, DIA has long pursued a global strategy for improving patient safety. DIA educational and networking forums provide the opportunity for industry, regulators, and patients to contribute to global standards and systems by sharing their experiences. We work very closely with the ICH, regional regulatory authorities, and other organizations throughout the world, so that these issues are illuminated and discussed. As Yves Juillet mentions in his President’s Message for this issue, DIA forums have advanced discussions on these and related topics, and, as a result, have helped advance drug safety throughout the world.
Efficient and Cost-effective Site Monitoring During Observational Studies

Ronald E. Weishaar

Approval from regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is necessary for biopharmaceutical companies to market their products. However, approval does not guarantee commercial success of the product. In addition to traditional clinical trials, stakeholders are now demanding that product effectiveness be evaluated, after the product is approved, in patients receiving the current standard of care from their physician.

As a result, the efficiency and reliability of newly approved drugs are increasingly being measured in postapproval observational studies. While clinical trials typically involve relatively small numbers of patients and stringent controls, observational studies evaluate effectiveness in a noninterventional, real world setting.

In the observational study environment, the researcher does not control the experiment, administer the study drug, or have protocol-driven visit or sampling requirements. The physicians involved with the study typically have little or no experience with clinical research. Compared to preapproval clinical trials, observational studies evaluate more patients to better assess the product’s side effects and safety profile.

Even though observational studies are conducted with fewer controls than clinical trials, timely and credible data is extremely important. There are currently different approaches to monitoring site performance to ensure data integrity. This article reviews the different approaches to monitoring and provides recommendations to maximize the productivity of your studies in a cost-effective way.

Intense Monitoring
This approach, which is commonly implemented to monitor site performance during randomized clinical trials (RCTs), requires inspectors to visit physicians and their staff onsite every six to eight weeks to investigate all aspects of patient enrollment and treatment, examine study drug inventory and reconciliation logs and evaluate data collection and case report form (CRF) completion procedures. Although efficient for RCTs, this approach is impractical and costly for observational studies which typically last for many years and involve thousands of sites across many different countries. In addition, patients participating in observational studies receive commercially available medications, eliminating the need for study drug inventory and reconciliation logs. CRF review is also generally not required since electronic data capture (EDC), a technique which typically involves the collection of information, clinical data and patient-reported outcomes via the Internet is extensively used for observational studies.

Limited Monitoring
Inspector onsite visits every six to twelve months can significantly reduce the cost of monitoring site performance for lengthy observational studies. However, this approach minimizes the interaction

Figure 1: The variety of site management tasks that can be successfully managed by a remote monitor engaging with their sites by phone, acting in a similar capacity as an air traffic controller monitoring the status of aircraft circling a control tower.
of physicians and their staff with inspectors, typically leading to deterioration of site performance both in terms of patient enrollment and data collection and entry. Due to the limited clinical research experience of physicians and their staff, they require frequent contact to ensure the necessary level of performance. An alternative approach is to ask sites to submit patient-related information electronically, by fax or email. This approach is effective for observational studies for the collection of retrospective information from a managed care database, as well as for studies involving abstraction of information from medical charts. However, it is inefficient for prospective observational studies, raising doubts with regard to the credibility of patient enrollment information and data collected.

Remote Monitoring
This is a balanced approach, where remote site monitoring is performed by telephone. Remote monitors are experienced clinical research associates (CRAs) who investigate whether sites are meeting performance expectations by checking indicators such as the time required to complete study start-up documents, the need for repeated training of study procedures and the amount and quality of data entered by EDC. This is a very effective approach, allowing reinforcement of desired behaviors such as enrolling patients, ensuring identification of all potential safety-related events and quickly triaging potential problems. However, remote monitoring cannot be used for tasks that require an onsite visit such as source document verification. The range of observational study tasks that can be monitored remotely by phone is shown in Figure 1.

Combining monthly remote monitoring with annual onsite visits can be particularly efficient for long-term observational studies such as registries (Figure 2). In those cases, the remote monitor is always designated as the site’s single point of contact, given the infrequency with which the onsite monitor visits the site. Taking this approach enables sites to frequently interact with their primary monitor while also allowing for yearly audits of key documentation. There are some prerequisites to ensure that this approach is as effective as possible. First, the remote monitor must be an experienced CRA capable of identifying early warning signs of potential problems. Secondly, an effective triage system must be implemented to ensure timely and appropriate response to early warning signs. Finally, additional out-of-cycle onsite visits should be made to sites experiencing difficulty meeting their study obligations.

Remote monitors can prove very effective for observational studies aimed at monitoring the long-term occurrence of serious adverse events (SAEs). Sites involved with such studies often over- or under-report SAEs due to their lack of experience with clinical research, their unfamiliarity with products new to their practices and/or their limited contact with their sponsor or monitor. However, a carefully designed remote monitoring approach can facilitate the early identification of possible safety-
the conduct of observational studies to monitor the effects of new drugs in a real-world setting. To ensure that costs are minimized and reliable results are generated, an efficient approach must be implemented to monitor the performance of sites involved with observational studies.

Different approaches can be taken to monitor site performance for observational studies. These range from an intense approach of frequent onsite monitoring performed by an experienced CRA to entirely remote monitoring via electronic methods. Remote monitoring can be combined with limited onsite visits to create a balanced approach that will provide an effective and cost-efficient means to audit documentation, assess site performance, triage problems and maintain employee motivation at the site. All approaches have advantages and disadvantages, and there is no single approach that will work for every type of observational study. Each option must be separately considered within the context of the study's objective and the purpose for which the resulting data will be used.

Figure 3: An example of how frequent interactions between the remote monitor and sites can reveal information regarding “safety signals” that might not otherwise be reported to the sponsor’s safety department, and how this information is triaged.

Conclusion
Increasing concerns about the safety and effectiveness of new biopharmaceutical compounds have led to an increase in related events. Figure 3 illustrates an example of this application of remote monitoring, where probing questions are used to obtain information about an “episode” that may not be an SAE. Subsequent discussion about the episode with an appropriate physician in Medical Affairs determines its potential importance, and in cases where the episode is designated as an SAE, it is reported to the sponsor’s safety department for further review. The remote monitor then investigates the occurrence of similar episodes in other sites and if it is required, supplemental training is initiated to ensure that this safety signal is being uniformly reported to the sponsor by the site in question.

Ronald E. Weishaar PhD, is Vice President, Observational Research, PharmaNet Development Group. Readers can contact him at rweishaar@pharmanet.com.
Clinical Trials in Emerging Latin American Countries
Addressing the Challenges

Karen Politis Virk

As biopharmaceutical companies continue to expand into new emerging markets in order to cut costs and meet growing requirements, several countries in Latin America have exhibited significant growth in outsourced clinical research. According to DataEdge market research, Latin America is currently the world’s fourth largest clinical trials market. The six most dominant countries in the region are Argentina, Brazil, Mexico, Chile, Colombia, and Peru. These countries account for more than 2/3 of the region’s population and approximately 70% of all clinical trials conducted in the region.

However, regulatory environments are still evolving, and disparities among different patient populations create ethical challenges. Last but not least, significant variations in regional Spanish and cultural differences among ethnic minority populations must be carefully addressed, especially in the preparation of patient materials. The focus of this article is primarily on increasing awareness and implementing strategies to overcome these barriers.

Disease Trends
The range of diseases occurring in these countries allows for a wide range of study. As a result of lifestyle changes, the incidence of cancer, heart disease and diabetes have increased markedly in Latin America as a whole. Both Chile and Peru reportedly have a high incidence of gastric carcinoma, and Peru has a high incidence of gallbladder cancer. Moreover, the incidence of cervical cancer is high throughout Latin America. Other types of cancers, such as breast, lung, and colorectal cancer have incidences similar to the U.S. and Europe. Infectious diseases primarily found in developing countries are also prevalent. In Peru, for example, there are a large number of treatment naïve patients with infectious diseases that have been eradicated in the U.S. and Europe. This provides the opportunity to access specialized patient populations for vaccine testing. Additionally, because the seasons in the Southern hemisphere complement those in the Northern hemisphere, this allows for many seasonal illnesses such as respiratory diseases to be studied year round. Finally, the large pediatric population - 30% of the population is reportedly under 14 years old - translates into a growing elderly patient population and potentially large new drug market.

Regulatory Environment
Although Brazil, Mexico and Argentina are clearly far ahead in the number of outsourced clinical trials as a result of their larger patient populations and more established regulatory environments (Brazil has the largest patient population followed by Mexico, and Argentina has the most evolved regulatory environment in Latin America), Colombia, Peru, and Chile are gradually becoming more established. Although each of these countries has a different regulatory approval process, there are some similarities. All of them function with both local and central ethics committees, and have a single regulatory agency responsible for regulating clinical trials (a branch of the Ministry of Health).

In all three countries, regulatory documents must first be submitted...
to Ethics Committees for approval, followed by approval from the national Ministry of Health. Although some countries in Latin America, e.g. Brazil, have made an effort to streamline approval processes and shorten timelines; Peru, Colombia, and Chile continue to have a sequential submission process. In Colombia the regulatory authority responsible for monitoring clinical research is the Instituto Nacional de Vigilancia de Medicamentos y Alimentos, and the average time for regulatory approval is 4-5 months 5. In Chile the Instituto de Salud Pública regulates clinical research and the average time for approval is approximately 3-4 months 5. In Peru the Instituto Nacional de Salud is the regulatory authority responsible for regulating clinical trials and the average time for regulatory approval is 5-6 months 5.

For the most part, clinical sites adhere to ICH-GCP guidelines as local regulations are aligned with the Declaration of Helsinki. However, sponsors have reported that more training and stricter monitoring need to be implemented. Despite this and the fact that regulatory environments are still evolving, there are several positive changes that indicate progress. For one thing, clinical investigators, clinical research staff and ethics committee training and requirements have improved. In addition, there has been an increase in the number of inspections of clinical sites. For example, in Peru, where both the local industry and the U.S. FDA (since 1996) have been involved in inspecting clinical trial sites, and as of 2000 all inspected sites have passed regulations 6.

Addressing the Challenges
In Peru, Chile and Colombia all regulatory documents must be provided in Spanish. Although the single translation requirement simplifies the preparation of regulatory documents, especially as compared to multilingual countries in Asia, variations of the Spanish language among these countries as well as the numerous regional dialects within each country must be carefully considered, especially when preparing patient materials. In addition to linguistic differences, cultural differences among ethnic patient populations must also be taken into consideration. Moreover, aspects of Latin American culture must be understood for effects on informed consent procedures. Many patient populations may have limited reading abilities and low economic status. In such cases, additional measures must be taken to ensure that patient rights are protected. Thus, conducting successful, quality trials in these Latin American countries is largely dependent on overcoming linguistic, cultural and socio-economic barriers.

Language Barriers and Translation
One of the biggest challenges, given that most studies originate in countries outside of Latin America, is language. Not only is careful translation critical to the logistics and procedures involved, it is even more crucial to ensuring the safety and ethical treatment of study participants — particularly in the area of informed consent. Addressing language barriers therefore requires an understanding of the patient demographics in each country. Although all regulatory documents must be provided in Castilian Spanish, the official and written language of the countries that we are discussing, any patient-related materials must be adapted for the target patient population. Experts who are native speakers and have a background in clinical research are best equipped to perform such culturally sensitive translations.

Due to the large geographic barriers in the region, several variants of Latin American Spanish have developed. Not only are there variations of Spanish particular to each of these three countries, but within each country there are distinct regional dialects. Often words from local indigenous languages have replaced Spanish words or there are different meanings for words or phrases. In addition, large immigrant groups have also influenced the way the language is spoken.

For example, the people of Peru predominantly speak three different languages: Spanish, Quechua, (both of which are official languages) and Aymara (also widely spoken). The Spanish spoken in Peru has two forms or dialects, the Spanish of the coast and that of the central capital region. Quechua, the official language of the Incas, has had a great influence on Peruvian Spanish and
several words from this indigenous language have permanently been introduced into the Peruvian Spanish language, e.g. papa (potato) and alpaca (llama wool).

This same is true of Chilean Spanish. Not only are there important differences in pronunciation, syntax and vocabulary between Chilean Spanish and other Latin American forms of Spanish, but regional differences are also significant. Guata (stomach) and guagua (infant) are examples of words adopted from Quechua which is mostly spoken in northern Chile. Other indigenous words that have entered Chilean Spanish originated from Aymara, predominant in the Andean north (such as phalta meaning avocado rather than the word aguacate used in much of Latin America) and Mapudungun which is most common in southern Chile.

In Colombia there are about 65 indigenous languages and nearly 300 dialects. Colombian Spanish is a mixture of the Caribbean dialect and Peruvian coastal dialect. Many communities on the Colombian coast have their own idioms and local usages as a result of different influences. Translators must take these differences in word use or meaning into account to avoid misunderstandings. For example, in Colombia, the formal you (usted) and informal you (tú) are not only interchangeable, unlike Castilian Spanish, but they are used to address people in a way that is unique from other variations of Spanish.

Dominant indigenous populations and large immigrant groups have not only influenced the way the language is spoken in each of these countries, but they are also responsible for differences in the local culture. Among the most common reasons for delays by ethics committees are problems with informed consent, and these are often associated with poor translation. In large part, this can be avoided if linguistic and cultural differences are properly addressed.

In addition, obtaining informed consent according to the ethical guidelines set by countries established in clinical research is often challenging due to cultural differences. For example, unlike the U.S., patients in Latin America generally tend to accept the recommendation of their physician without question. As a result, patients may accept to participate in a clinical study without discussing other treatment options or potential risks with their physician. The challenge therefore is one of reconciling these differences in such a way that foreign sponsors respect the local culture while protecting patient rights. The solution lies largely in properly addressing linguistic and cultural differences.

Socio-economic Factors
Despite the fact that health systems vary from country to country, there is a distinction between public and private institutions. Although both can conduct clinical trials in these countries, there are epidemiological, socio-economic and cultural differences depending on the patient population. These factors, relevant to selecting a site for a specific clinical trial, also create an ethical dilemma for sponsors. For example, despite the fact that there have been efforts to improve health care coverage in some countries - in 2010 Peru approved universal health insurance, Chile’s 2005 health care reforms mandated greater health care coverage and 1993 health care reforms in Colombia pushed more universal coverage - many patients still do not have access to adequate health care or newer treatments. In many cases, their only treatment option may be that provided by clinical trials. As this makes them more vulnerable, measures must be taken to ensure that they are adequately informed of potential risks and that informed consent is obtained ethically.

In addition, because of their low socio-economic status, some patients have limited reading skills. In Peru, the country’s literacy rate has reportedly improved with recent economic growth, and illiteracy has dropped to 7.1% 6. In Colombia literacy rates are reported at 90.4% and in Chile it is 95.7% 7. However, these statistics vary among different patient populations. For example, women tend to have a higher rate of illiteracy in these countries as do ethnic minority populations and individuals from rural areas. Furthermore, although some patients may not be considered illiterate, they may have a limited understanding
of medical concepts or poor reading comprehension. Many indigenous populations face prejudices that interfere with their ability to access adequate health care and education. Despite efforts to protect the rights of these vulnerable patient populations by ethics committees, this issue constitutes a major challenge. Socio-economic barriers to obtaining ethical and voluntary informed consent, however, can be overcome if sponsors work closely with investigators and clinical trial staff to communicate expectations.

Conclusions
Over the last decade, the annual investment in the clinical trial sector in Latin America’s Andean Region has increased from $3-4 million to more than $50 million per year. Although Brazil, Argentina and Mexico continue to have more significant growth due to their larger patient populations and more established regulatory environments, clinical research in Peru, Colombia and Chile has also shown significant growth.

As the number of outsourced clinical trials continues to increase in these three countries, sponsors must address significant challenges, including linguistic, cultural, and socio-economic barriers. Despite the single translation requirement, there are variations of Spanish as well as regional dialects in each country that must be considered, especially when translating patient materials such as informed consent. Cultural differences and socio-economic factors that interfere with informed consent must also be taken into account. If these barriers are properly addressed, not only will patients be better protected, but the quality of clinical trials and health care will ultimately be improved in the region.

References

Karen Politis Virk is Director of Biotech & Pharma Research at Language Connections, Boston, MA. Readers can contact her at karen@languageconnections.com.
The pressure to get to market quickly means companies are now depending increasingly on access to high-quality information. This is as true in the pharmaceutical industry as in other sectors, although it has taken longer for life sciences organizations to realize this than it has taken companies in, say, the financial services sector.

Now, however, the pressure to meet new regulatory requirements—along with the drive toward electronic submission—has necessitated a more robust information management strategy here too. Despite that, many companies are investing only when and where they have to rather than embracing information management for strategic, competitive advantage.

So, what is the way forward? How can companies derive greater return on investment from their attempts to satisfy regulatory information management (IM) requirements?

From Information to Insight
It’s one thing to collect and store information, but that doesn’t automatically lead to use of information in valuable ways. Organizations often capture and hold so much data that they get paralyzed by it. Held in multiple silos across the enterprise—and frequently overlapping—the content cannot be relied on to provide a single, clear view of a situation, thereby making it worthless.

Pharmaceutical organizations know this. A series of focus groups conducted for regulatory software and services consultancy ISI* confirmed that even where life sciences companies have captured information stored in enterprise information and document management systems, typically the content is unintegrated, and therefore, it cannot be harnessed effectively.

This situation must change. Regulators now expect and demand that pharmaceutical companies be able to find critical product information quickly and reliably. It means an audit trail must exist across the life cycle of every drug, ensuring and demonstrating compliance with safety measures—and enabling swift product recalls.

On one hand, unless all of the relevant information gets captured and managed consistently and accurately, organizations are exposed to risks: risks of noncompliance, risks of having products withdrawn from the market, and risks of jeopardizing patient safety. On the other hand, once they have mastered holistic information management, they have both covered themselves and acquired something valuable that the business can potentially exploit in additional ways.

Regulatory IM
Regulatory IM is the management of all of the information related to global product licensing, marketing, and maintenance—everything required to monitor the licensing requirements and product status for every drug sold in every market, thereby keeping authorities satisfied and patients safe.

The potential scope of Regulatory IM is much broader, however. A comprehensive Regulatory IM strategy should also incorporate submission management, registration management, portfolio management and resource planning.

Competitively, life sciences organizations need to achieve speed to market and lower costs of entry while maintaining standards. With the growing move toward market expansion, companies must also find ways to contain the complexity and costs of tracking and managing applications and registrations in each country, especially given that regulatory requirements often differ wildly from one market to the next—particularly across Europe. Without reliable systems to take the strain and ensure accuracy, the associated administrative burden is potentially draining.

Life Cycle Management
While specialist software tools can certainly help, it is not enough to throw technology at the problem. Supportive information technology systems not only have to be accepted and used willingly and correctly by staff across diverse parts of the organization; such systems also need to be tuned to and implemented in line with optimized business processes—those that promote efficient and reliable information sharing and that offer improvements in productivity and efficiency.

Regulatory IM demands that all individual regulatory requirements and processes be served from a single point of integration. Even if
the data originates across separate systems, it must be easy to extract for comparison against or blending with other, related content.

A comprehensive solution will incorporate as well registration planning and tracking (identifying, for example, which tests will be needed to complete an application for a new product in a new market and how the organization will manage the required activities); submission planning, publishing, and tracking; registration management (beyond initial license approval); and high-level portfolio management.

Vigilance beyond the initial drug application or marketing authorization application is crucial. In other words, maintaining the license in the market as changes get made to manufacturing specifications or as the license has to be updated is vital.

**Forward Planning**

An organization’s Regulatory Information Management system should also enable commercial managers to see high-level information. Such access shows them how and where the business can expand, so they can determine the focus and direction of the company and can map out commercial plans for the years ahead.

An independent survey conducted last year by health care consulting firm Gens and Associates** found that more than 70 percent of respondents still use manual tracking and spreadsheets to generate reports. Most companies use a combination of tools to manage and track information, and the tools are applied in a disjointed way.

In the ISI focus groups, meanwhile, pharmaceutical organizations admitted they were struggling with even the most basic information—such as knowing which products were registered where. In other cases, the problem is simply that Regulatory IM has until now been addressed as a series of discrete activities, driven by specific questions around submissions, obligations (eg, scheduled items such as annual reports or manufacturing changes), or marketing authorization status.

**Involving Users**

As companies strive toward connected regulatory IM—as many now claim to be doing—it’s important that they consider and involve the information users so as to make sure that any new processes and systems reflect the way users need to work.

For some companies, it may be easiest to start over rather than battle to bring old, legacy systems in line with current information demands. Starting over would give wider scope to exploit the information that companies are collecting to fuller commercial advantage.

Until now, the majority of tracking tools in use by life sciences organizations have neither incorporated planning nor facilitated the integration of multiple sources of data. This has limited the potential impact of the information that companies are monitoring. As their target markets become increasingly global, the need to track and plan more strategically becomes paramount—and far beyond the scope of simple spreadsheets. Happily, this is now beginning to change. Gens reports that many companies are preparing to make organizational and procedural changes to submission operations over the next two years, with a significant investment being made by the top 60 pharmaceutical organizations globally in submission management registration tracking projects. Among the top 30 companies, as many as 88 percent are now making significant changes to their submission management activities, with the aim of benefiting from the ability to engage in more predictable planning.

Reasons given include the need to support electronic Common Technical Document (eCTD) submissions as well as opportunities in emerging markets. Companies now want an authoritative source of information concerning registrations and product files.

Cost reduction is a big driver, too, along with the need for data mining...
A lot rides on this: companies’ abilities to respond to new market opportunities, adapt to changes, and comply with increasingly stringent regulations while maintaining their competitive edge.

Because capturing and ensuring the quality, accuracy and availability of regulatory data is mandatory, not doing more with it seems a great waste.

Sources
*Findings of a series of focus group meetings held in Europe and the United States with ISI’s Client Advisory Board members and a panel discussion held at ISI’s September 2009 eSolutions Conference in Barcelona, Spain
** 2009 Bio-Pharmaceutical Submission Management Survey

Gillian King, Director, Head of Global Consulting, Regulatory Solutions Group - CSC Life Sciences

Readers can contact Gillian at gking@csc.com, www.csc.com.

Building the Business Case
The cost of poor information management can be high. Commercially, it could mean protracted, inefficient and costly administrative processes; delays in getting to market; and failure to maximize revenue opportunities.

While budgets might have created a stumbling block to information consolidation initiatives in the past, in today’s climate, Regulatory IM systems are as integral to a company’s needs as an SAP system is to planning finances—because regulatory information represents the company’s intellectual property.

To strengthen the business case, companies should consider who the different stakeholders are across the organization and how each will benefit. For example, a comprehensive Regulatory IM solution would enable the regulatory affairs team to see which products are registered where; to respond to queries; and to become confident that the information registered is current and reflects what is actually being manufactured.

The compliance team would be able to see where individual products are and determine the impact of any changes globally. The regulatory operations team would be able to use planning and tracking to better manage resource allocation for submission compilation. And the commercial side of the business would know when a product had been approved and licensed, enabling it to initiate marketing plans.

Process Improvements
While a well-designed technology solution might substantially simplify Regulatory IM, its impact will not be felt unless it is matched by optimized processes. Similarly, users will need to buy in to the new system, which means communicating the benefit in terms they will understand and then training them to use the technology with confidence.

From a regulatory perspective, life sciences organizations have little choice but to hone their information-recording/tracking capabilities. The same applies if they want to expand their markets globally, maximize relationships with affiliates, and minimize the disruptive impact of mergers and acquisitions.

Holistic information management involves achieving a single version of the truth, being able to release and share content more readily, and ultimately driving more efficient processes, workforce enablement, and decision support.

capabilities as companies look for greater control of in-licensing and divestitures and as they generally strive to manage more effectively and more efficiently their global capabilities.

To strengthen the business case, companies should consider who the different stakeholders are across the organization and how each will benefit. For example, a comprehensive Regulatory IM solution would enable the regulatory operations team to see which products are registered where; to respond to queries; and to become confident that the information registered is current and reflects what is actually being manufactured.

The compliance team would be able to see where individual products are and determine the impact of any changes globally. The regulatory operations team would be able to use planning and tracking to better manage resource allocation for submission compilation. And the commercial side of the business would know when a product had been approved and licensed, enabling it to initiate marketing plans.

A lot rides on this: companies’ abilities to respond to new market opportunities, adapt to changes, and comply with increasingly stringent regulations while maintaining their competitive edge.

Because capturing and ensuring the quality, accuracy and availability of regulatory data is mandatory, not doing more with it seems a great waste.

Sources
*Findings of a series of focus group meetings held in Europe and the United States with ISI’s Client Advisory Board members and a panel discussion held at ISI’s September 2009 eSolutions Conference in Barcelona, Spain
** 2009 Bio-Pharmaceutical Submission Management Survey

Gillian King, Director, Head of Global Consulting, Regulatory Solutions Group - CSC Life Sciences

Readers can contact Gillian at gking@csc.com, www.csc.com.

Building the Business Case
The cost of poor information management can be high. Commercially, it could mean protracted, inefficient and costly administrative processes; delays in getting to market; and failure to maximize revenue opportunities.

While budgets might have created a stumbling block to information consolidation initiatives in the past, in today’s climate, Regulatory IM systems are as integral to a company’s needs as an SAP system is to planning finances—because regulatory information represents the company’s intellectual property.

To strengthen the business case, companies should consider who the different stakeholders are across the organization and how each will benefit. For example, a comprehensive Regulatory IM solution would enable the regulatory affairs team to see which products are registered where; to respond to queries; and to become confident that the information registered is current and reflects what is actually being manufactured.

The compliance team would be able to see where individual products are and determine the impact of any changes globally. The regulatory operations team would be able to use planning and tracking to better manage resource allocation for submission compilation. And the commercial side of the business would know when a product had been approved and licensed, enabling it to initiate marketing plans.

Process Improvements
While a well-designed technology solution might substantially simplify Regulatory IM, its impact will not be felt unless it is matched by optimized processes. Similarly, users will need to buy in to the new system, which means communicating the benefit in terms they will understand and then training them to use the technology with confidence.

From a regulatory perspective, life sciences organizations have little choice but to hone their information-recording/tracking capabilities. The same applies if they want to expand their markets globally, maximize relationships with affiliates, and minimize the disruptive impact of mergers and acquisitions.

Holistic information management involves achieving a single version of the truth, being able to release and share content more readily, and ultimately driving more efficient processes, workforce enablement, and decision support.
I am pleased to introduce the following articles on drug safety and pharmacovigilance, covering a range of topics that should resonate with readers who work in this area. They have been written by various members of the Clinical Safety and Pharmacovigilance SIAC for this edition of the Global Forum; thanks to all the authors for their contributions.

Managing Potential Safety Signals Detected Through Quantitative Methods
A major challenge associated with the introduction of quantitative signal detection techniques within an organization has always been the large number of potential signals arising from the application of these techniques. Many of these initial potential signals can be dismissed relatively easily, but due to the large number of initial signals, this still represents a significant amount of effort. This article discusses ways to address this challenge, including the use of statistical techniques.

Integrating Signal Detection in the Pharmacovigilance System: Key Practical Aspects from the CIOMS VIII Report
Signal detection relies upon information that has been previously identified, collected, and processed; that is, it depends on previous, existing pharmacovigilance activities. However, since these signals must be prioritized and communicated, signal detection must be integrated with existing PV systems. This article reviews traditional and current signal detection methods and offers points to consider when implementing a new method.

Strategies to Uncover Troublesome Embedded Adverse Events
Understanding the complete safety profile of a drug depends on postmarketing surveillance and spontaneous reports of adverse events (AEs) which occur after the drug is approved and begins to be used by a broad patient population. The most critical component of these reports is the ability of the contact center agent to uncover the full story of the AE so that it can be evaluated for medical significance. In this article, the author discusses ways of identifying embedded AEs from product complaints and medical inquiries.

The Importance of Proper Training in Terminologies for Quality Coding and Its Impact on Data Analysis
Pharmacovigilance and the capture of data in the health care/life sciences context often involve the use of many diverse terminologies. Because numerous terminologies exist, this article focuses on the ones described in the Medical Dictionary for Regulatory Activities (MedDRA), and the World Health Organization’s Drug Dictionary (WHO-DD). It also references the International Classification of Diseases (ninth revision).

The Developmental Safety Update Report: The New Way to Drug Safety or a Born-again Old Report?
The ICH E2F guideline on Development Safety Update Reports was finalized in August 2010 with the aim of providing “a common standard for periodic reporting on drugs under development among the ICH regions” so that the same document could be submitted to all regulators. This article explores the question of how things have changed since the author first wrote his first ASR.

Effectiveness of REMS Tools
In 2007, the Food and Drug Administration Amendments Act was signed into law, authorizing the FDA to require a Risk Evaluation and Mitigation Strategy from drug manufacturers, if necessary, to ensure that the potential benefits of a drug outweigh its risks. At the time of this writing, 185 REMS have been approved by the FDA. This article presents information on which REMS elements have influenced prescriber and patient behaviors and led to reduced product risks in patients.

Steve Jolley is Principal, SJ Pharma Consulting. He also serves as Co-chair of the DIA Clinical Safety & Pharmacovigilance (CSP) SIAC. Readers can contact Steve at steve@sjpharmaco.com.
MANAGING POTENTIAL SAFETY SIGNALS DETECTED THROUGH QUANTITATIVE METHODS

Robbert P. van Manen

“...in the field of observation chance favors only the prepared mind.”

Introduction
Quantitative safety signal detection has gradually become a common practice in pharmacovigilance today. An important factor in this process is the increasing use of quantitative signal detection methods by regulatory authorities (FDA Pink Sheet, 2005), as well as emerging guidelines and regulations, such as the FDA Industry Guidance documents of 2005 (FDA, 2005), EMEA regulations (Alvarez, 2010) and PMDA projects (Mihari) with respect to signal detection by market authorization holders.

A major development in the US has been the signing of the Food and Drug Administration Amendment Act (FDAAA) of 2007, which includes several components, such as the Prescription Drug User Fee Act IV (PDUFA IV) and the Medical Device User Fee and Modernization Act (MDUFMA). PDUFA IV requires the FDA to have 25 million patient records available for surveillance in 2010, and 100 million by 2012. Mandated by the FDAAA is also the Reagan-Udall Foundation, an independent private non-profit organization founded in 2007 to help support and promote the FDA’s regulatory science priorities. One of the objectives of this organization is defined as “the incorporation of more sensitive and predictive tools and devices to measure safety.”

In addition, several other initiatives focusing on the improvement of the safety of medicinal products are currently underway, both in the US and abroad. The FDA Sentinel initiative was launched in May 2008 by the FDA “to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products” (www.fda.gov). It is aimed at providing the FDA with access to electronic health records in order to evaluate possible medical product safety issues.

The Observational Medical Outcomes Partnership (OMOP) is a public-private partnership performing a series of studies to assess different types of data from across the United States, develop tools and methods to analyze the databases, and evaluate how analyses can contribute to decision-making.

The Mihari project of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) focuses on safety information from postmarketing studies on providing access to electronic medical health records, as well as developing methodologies to use these records for the assessment of the safety of medicinal products.

Another important step is the publication of the Report of CIOMS Working Group VIII “Practical Aspects of Signal Detection in Pharmacovigilance,” a comprehensive report containing guidelines for the development and implementation of quantitative signal detection methods.

A major challenge associated with the introduction of quantitative signal detection techniques within an organization has always been the large number of potential signals initially arising from the application of such techniques.
Many of these initial potential signals can be dismissed relatively easily, for example, as the result of confounding related to demographic factors, concomitant medications or underlying disease conditions. Due to the large number of initial signals, however, this still represents a significant amount of effort, which would have to be repeated each time the signal detection database has been refreshed with new data.

This challenge can be addressed in a number of ways, which will be discussed in detail in this article. It is possible to use statistical techniques to limit number of initial potential signals. In addition, potential signals can be prioritized intelligently on the basis of a combination of their intrinsic characteristics and information on prior decisions with respect to the same potential signal.

Once a potential signal has been detected through quantitative methods, additional statistical techniques may be employed for further confirmation and characterization of the signal. In addition, potential signals derived from one source, for example a spontaneous adverse reaction reporting database, may be corroborated using another source of information, such as longitudinal electronic health care records.

Sources of Potential Safety Signals and Their Characteristics
Product safety information can be obtained from a variety of different sources. The most commonly used sources are:

• Clinical trials
• Postmarketing spontaneous adverse reaction reporting
• Longitudinal health care databases

Safety Signals from Clinical Trials
The use of clinical trial data for the identification and analysis of potential safety signals offers a number of advantages.

• Most clinical trials collect very detailed information about their subjects, including, for example, laboratory and ECG data. In addition, this information is checked for completeness and consistency; therefore the data is (usually) of high quality.

• Subject exposure in a clinical trial is well documented, providing a direct basis for adverse event incidence calculations.

• Often a control group is available, making it possible to perform direct comparisons to exposed and unexposed or control populations.

Clinical trials also have a number of disadvantages as a source of safety information.

• Compared to the target market, the number of subjects in a clinical trial, or even in a set of pooled clinical trials for a product, is usually small, making it impossible to reliably detect rare adverse reactions.

| Power: Probability that the mean event rate is greater than that specified (most commonly used values are 0.9 or 0.95) |
| Mean event rate Lambda (λ): Rate of occurrence of the adverse event |
| Critical tolerance limit r: The number of positives which if occurring within the sample size, will support the conclusion that the prevalence is greater than the mean event rate λ (the most commonly used value is r=1, so that as soon as a positive event occurs, a conclusion can be drawn) |

Sample sizes for rare events

<table>
<thead>
<tr>
<th>power</th>
<th>λ</th>
<th>r</th>
<th>ssiz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>0.01</td>
<td>1</td>
<td>231</td>
</tr>
<tr>
<td>0.95</td>
<td>0.01</td>
<td>1</td>
<td>300</td>
</tr>
<tr>
<td>0.99</td>
<td>0.01</td>
<td>1</td>
<td>461</td>
</tr>
<tr>
<td>0.90</td>
<td>0.001</td>
<td>1</td>
<td>2303</td>
</tr>
<tr>
<td>0.95</td>
<td>0.001</td>
<td>1</td>
<td>2996</td>
</tr>
<tr>
<td>0.99</td>
<td>0.001</td>
<td>1</td>
<td>4606</td>
</tr>
<tr>
<td>0.90</td>
<td>0.0001</td>
<td>1</td>
<td>23026</td>
</tr>
<tr>
<td>0.95</td>
<td>0.0001</td>
<td>1</td>
<td>29958</td>
</tr>
<tr>
<td>0.99</td>
<td>0.0001</td>
<td>1</td>
<td>46052</td>
</tr>
</tbody>
</table>


The exposed population in a clinical trial is often not a direct representation of the actual population exposed once the drug is on the market. The use of inclusion and exclusion criteria often precludes the assessment for safety for special populations, such as elderly or pediatric subjects or subjects with a specific medical history or concomitant medications.
Safety Signals from Spontaneous Adverse Reaction Reporting
Advantages of the use of postmarketing spontaneous safety reporting databases are

- A spontaneous safety reporting database represents real-world product use, including, for example, special populations and off-label use.

- For the submission of a spontaneous adverse reaction report, an explicit causal link between product and adverse reaction has been assumed by the reporter, therefore there is no need to infer causality implicitly on the basis of for example chronology of events.

- Many spontaneous safety reporting databases are publicly available, for example the FDA AERS and VAERS databases, which are made available free of charge under the US Freedom of Information Act (FOIA), or the WHO Vigibase database, which can be licensed from the World Health Organization.

Disadvantages of the use of postmarketing spontaneous safety reporting databases are

- A spontaneous adverse reaction report usually offers only a snapshot in time: only very limited or no information is provided about the subject’s medical history, and apart from formal follow-up reports, very limited information about the long-term development of the subject’s condition is available.

- Spontaneous safety reports often contain incomplete and/or inconsistent information; generally, the quality of the data is significantly lower than that of clinical trial data.

Safety Signals from Longitudinal Health Care Databases
Longitudinal databases of health care information, such as those maintained by Health Management Organizations, have important advantages.

- Longitudinal health care databases generally contain information about very large numbers of subjects – often many millions, much more than the limited numbers of subjects in clinical trials, and usually also more than spontaneous reporting databases.

- In addition to including large numbers of subjects, longitudinal health care databases usually cover subjects for significant periods of time, as compared to the limited duration of clinical trials or the snapshot in time represented by a postmarketing spontaneous adverse reaction report.

- Longitudinal health care databases represent real-world usage of the product under investigation, not a carefully selected population as would usually be the case in clinical trials.

Longitudinal health care databases also pose their own specific challenges, however

- Since longitudinal health care databases, among other things, are often used for reimbursement purposes, diagnoses or indications may have been adapted to obtain optimal reimbursement, thus not accurately representing the actual medical condition, a phenomenon known as “up-coding”.

- Contrary to spontaneous adverse reaction reporting databases, longitudinal health care databases usually do not contain explicit causal links between drugs, vaccines or devices on one hand and adverse reactions, diagnoses or indications on the other hand. It is, therefore, necessary to derive a potential causal relationship indirectly through analysis of the timing of the occurrence of an adverse reaction in relation to the subject’s exposure to the product. However, the fact that often information is available for very large number of subjects may positively contribute to the statistical strengthening of such temporal relationships.

Other Sources of Safety Information
Several other sources of safety information exist, for example safety assessment on the basis of pharmacological and toxicological characteristics of the chemical entity or the class of drug.

Another example of an alternative source of safety information is the use of the chemical and physical characteristics of a substance in relation to spontaneous adverse reaction reports. Particularly for a new chemical entity with only limited population exposure, it can be useful to assess potential side
Extended Logistic Regression

The traditional statistical approach to logistic regression exhibits an important flaw when applied to drug and device safety information: the logit curve, which represents the influence of a specific covariate on the occurrence of a specific outcome (adverse event), is linear around probability values of 0.5; however, in the usually much lower probability range of drugs and adverse events, the logit curve is not linear, but more exponential in shape. Whereas a linear logit curve represents an additive effect of multiple treatments, an exponential curve represents a multiplicative effect.

Stratification example: Pediatric adverse events and pediatric drugs

| Palivizumab (Synagis)* and “Weight gain poor” (AERS 2010Q2): N = 8 |  |
|---|---|---|---|
| Unstratified | Stratified |  |
| RR | 24.3 | 0.704 | (frequentist disproportionality score) |
| EBGM | 9.08 | 0.736 | (Bayesian disproportionality score) |
| EB05 | 4.02 | 0.423 | (lower 5% of EBGM confidence interval) |

In SRS + AERS 2010 Q1, stratification eliminates 49% of drug-event combinations with a disproportionality score (EBGM) over 2.0

* Prevention of Respiratory Syncytial Virus (RSV) infections

Effects in relationship with the chemical and physical characteristics of the product by looking at the disproportionality scores in postmarketing databases of other products with similar physical or chemical properties.

**Statistical Methods for Limiting the Number of Initial Safety Signals**

Reducing the number of initial signals generated has a positive effect on the complete downstream workflow. One of the methods to achieve this focuses on reducing the number of false positives generated due to confounding factors such as demography or timing.

False positives may be generated due to the fact that the prevalence of both a medicinal product and an adverse event is high in a specific subgroup, for example, due to demographic factors such as gender, age or ethnicity. The occurrence of such false positives due to confounding factors can be addressed through a statistical technique called stratification. Stratification involves the calculation of expected counts for individual strata based on confounding variables such as gender and/or age group. These expected counts will take into account the confounding factors used to create the strata and will thus minimize the number of false positives due to these confounding factors.

**Methods for the Statistical Assessment of Safety Signals**

Quantitative safety signal detection methods are hypothesis-generating only; therefore, once a safety signal has been initially identified, it will need to be confirmed as well as researched further. A number of statistical methods are available to characterize a signal in more detail and identify possible confounding influences, such as drug interactions or population effects.

**Logistic Regression**

The most widely used method is logistic regression, which makes it possible to assess the effect of individual covariates on a specific outcome while eliminating the effect of other, confounding covariates.

Experience has shown that a linear logit curve, representing an additive effect, provides a much more appropriate representation of drug-event relationships than a nonlinear curve (DuMouchel, 2007).
A potential solution to this problem involves the use of a spline-fitting procedure to adapt the logit curve in such a way that it is linear within the range of probabilities applicable to the drug-event combination under investigation.

Identifying and Analyzing Drug Interactions

The average number of different medicinal products used by a single patient tends to increase with age, an effect which is amplified by an aging population as well as the fact that polytherapy has become much more common over time. For this reason the identification of possible interactions between different treatments has become ever more important. An approach developed by Yang compares the co-occurrence of an adverse event with individual products with the co-occurrence of the same adverse event with a ‘pseudo-drug’ representing situations where both products occur together (Yang, 2004).

In addition, experience has shown that the traditional statistical approach for identifying interaction terms, which assumes a multiplicative effect, is not applicable to the way drugs interact. An alternative, much simpler, but highly effective representation of interactions, the Interaction Signal Score or INTSS, has been proposed by DuMouchel (DuMouchel, 2008). This score is calculated by dividing the lower boundary of the 90% confidence interval of the empirical Bayesian disproportionality score for the combined products with highest of the two the upper boundaries of the confidence intervals of the same score for the individual products by themselves. The result can be interpreted as an assessment of the probability that the effect of the combined products can be completely explained through the effect of either one of the products without an additional interaction effect. The figure in the lower left shows interactions between acetaminophen and ethanol for hepatic failure (INTSS = 3.745), hepatocellular injury (INTSS = 2.593) and hepatic function abnormal (INTSS = 2.285).

Managing Signals: Prioritization, Workflow and Documentation

Signal Management

One of the most important problems facing companies embarking on quantitative safety signal detection is the vast number of potential signals they are initially confronted with – and which they will continue to be confronted with in the absence of adequate signal filtering and prioritization capabilities.

Signals can be filtered and prioritized on the basis of a number of characteristics.

- Intrinsic signal characteristics
  - Number of case reports
  - Statistical parameters such as disproportionality scores, p-values, etc.
  - Labeledness/listedness/expectedness
• Previous decisions, for example, the fact that an adverse event is related to the drug indication

• Trends, for example, increases exceeding a certain threshold in disproportionality scores or numbers of case reports

**Signal Workflow**

Dependent on company size and signal complexity, multiple people may get to work on a potential signal, requiring an environment which provides functionality to support signal workflow management, for example:

• Signal status definition and controlled status transitions

• Workflow data elements with status-dependent roles (e.g., invisible, read-only, enterable, mandatory)

• Assignment of signal-related tasks to individuals and/or groups with associated deadlines

• Definition of subtasks associated with a signal

**Signal Tracking and Documentation**

An environment that offers powerful exploratory capabilities for identifying and analyzing potential safety signals should also make it possible to document exploration and analysis activities in an easy and user-friendly fashion. Documentation related to a potential signal can either be generated within the signal detection environment, for example, tables of signal scores or graphical representations of a potential signal; or it can originate from external sources, for example, references to scientific publications on the internet or clinical trial data in data files. It should be possible to combine both types of information seamlessly in a single potential signal documentation set, with appropriate tools for sharing and archiving the information at any given point in time, as well as audit trail functionality to track access to and modification of this information.

**Resources**


DuMouchel, William A New Family of Link Functions Extending Logistic Regression Joint Statistical Meetings, Salt Lake City, 2007

DuMouchel, William Data Mining for Drug Safety

Statistical Analyses of Spontaneous Reports, Clinical Safety Data, and Longitudinal Medical Records Rutgers University Biostatistics Day, February 22, 2008

FDA Increasing Use of Data Mining To Detect Early Safety Signals The Pink Sheet, 2005; 67 (048): 9

Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment FDA CDER, CBER, 2005

Guidance for Industry Premarking Risk Assessment FDA CDER, CBER, 2005

Guidance for Industry Development and Use of Risk Minimization Action Plans FDA CDER, CBER, 2005

Yang, XM Using disproportional analysis as a tool to explore severe drug-drug interactions in AERS database Pharmacoepidemiology and Drug Safety, 2004; 13 Supplement 1: 247

Robbert P. van Manen, MSc, is Master Principle Sales Consultant, Oracle Health Sciences Global Business Unit, The Netherlands. Readers can contact him at rob.vanmanen@oracle.com
INTEGRATING SIGNAL DETECTION IN THE PHARMACOVIGILANCE SYSTEM: Key Practical Aspects from the CIOMS VIII Report

Giovanni Furlan

When I first became aware of the release of the CIOMS VIII Working Group report, I was very excited, anticipating a technical, but easily understandable document detailing the mathematics underpinning statistical signal detection methods. I thought I would have a chance to understand the calculations required by Bayesian methodology (I had tried it in the last few years, with little success). My expectations, however, did not match reality, since only a part of one of the ten chapters (and five appendixes) of CIOMS VIII provides an overview of the various signal detections methods.

Why Were My Expectations so Far from Reality?

Signal detection (ie, the act of looking for information which suggests a new adverse reaction, or new aspects of an already known adverse reaction, and that is sufficiently convincing to justify some action being taken to prove or disprove the association between a drug and an adverse event) is not a stand-alone exercise. It relies upon already available information that has been previously indentified, collected and processed: therefore, it depends upon the pharmacovigilance activities, such as case processing and literature screening, that are performed to produce the data used for signal detection itself. Furthermore, once identified, signals need to be prioritized, evaluated, communicated and minimized. For this reason signal detection needs to be integrated and harmonized with the overall pharmacovigilance system and processes.

The CIOMS VIII report reflects the above and provides an overall view of the aspects that need to be considered by an organization in developing an effective signal detection strategy.

The first step for choosing the method that best fits the organization’s characteristics is to be aware of the key factors and limitations of signal detection methods.

Sensitive or Specific?

First, keep in mind that there is no gold standard and no signal detection method that is superior to another. The strength of this assessment is confirmed by there not being a recognized method for evaluating the performance of data mining. Therefore, if someone claims universal superiority of a certain signal detection method, it is likely that this statement is driven by a conflict of interest.

Most of the discussions on the superiority of one signal detection method over another are about sensitivity and specificity. In signal detection, sensitivity can be defined as the ability to correctly identify a numerical result (ie, the number of times a certain drug event association is reported) above a preset threshold as a signal, while specificity is the ability to correctly identify drug-event associations that do not reach the preset threshold and, therefore, are not signals.

The reason for these discussions stems from there being a trade-off between generating false positive signals (due to the threshold being too low) and missing potential signals in every signal detection method. However, the best balance between sensitivity and specificity depends on many factors, including the number of adverse reaction terms being screened, and the characteristics of the adverse reactions, of the dataset and of the drugs that are being screened.

Qualitative or Quantitative?

Traditional or Modern?

Traditional signal detection methods mostly use a qualitative approach and are based on the routine review of the received individual case reports by trained pharmacovigilance professionals. These methods rely upon the skills and knowledge of qualified personnel who should have an in-depth comprehension of the drug pharmacology, the indication for which it is being used, the characteristics of the population who uses it and of the adverse events which have a high drug-attributable risk over multiple therapeutic classes (such as Stevens-Johnson syndrome or torsades de pointes).

These approaches put a premium on sensitivity over specificity and are particularly important in the assessment of rare events. In fact, since every report is evaluated, a signal may be identified even...
from one well documented case having strong evidence of causality. Furthermore, they may be the best methods to use for small or specialized datasets (where a therapeutic area or an adverse event is over-represented) or during the period immediately after product launch.

Among the traditional signal detection methods, CIOMS VIII only mentions quantitative non-statistical methods, albeit they probably are still widely used. In this way the reviewer analyzes summary tabulations and compares the number of the most recently received adverse event terms with the cumulative ones. The threshold of the number of adverse event terms necessary to constitute a signal is arbitrarily set by the reviewer, but it can be adapted to the database size and characteristics.

However, for datasets containing tens of thousands of adverse reaction reports, an only-qualitative approach cannot be applied since it is unlikely the pharmacovigilance professional has evaluated all the cases associated with a certain drug and remembers all of them enough to be able to link a case report with a similar one that has been previously reported. Furthermore, reviewing long lists of adverse reaction terms might be unpractical, and the subjectivity of setting the threshold can be criticized and might be influenced by reviewer’s bias. In these instances, more complex quantitative methods should be used to enhance the effectiveness of qualitative and traditional quantitative methods by supplementing them with statistical analysis whose objective is to identify statistically prominent drug-event associations within a drug safety database.

**Statistical Signal Detection Methods: Caveats**

Statistical signal detection methods are based on weak assumptions, relating to the number of reports that are “expected” to be reported in the database. For example, they assume that if a specific drug causes a certain adverse reaction, this reaction will be reported more often for this specific drug than for other drugs or that the overall pattern of adverse reaction contained in the database is a valid reference against which to compare specific drug-adverse reaction combinations. Unluckily these assumptions are not always true. It should always be kept in mind, instead, that the statistical analysis of drug-event associations only provides another perspective of the reporting behavior at a certain point in time. The reporting behavior can be influenced by a high awareness of safety concerns due to media attention or regulatory action, by high reporting rates in the first years after products launch, by cultural attitudes, by marketing maneuvers trying to show the superiority of a drug over another, etc.

The results of data mining are not only influenced by the reporting attitude, but also by the size of the database and the different type and number of drugs and adverse reactions it contains. If the database is small and contains adverse reaction reports for only a limited number of products, results of statistical signal detection methods can be so distorted that their use is not recommended. Furthermore, the quality of the data, their processing conventions and the characteristics of the database need to be considered. For example, erroneous adverse reaction or medicinal product coding, coding adverse reaction signs and symptoms or diagnosis, the presence and number of duplicates contained in the database, coding the medicinal product brand and/or non proprietary name, the migration of individual case safety reports that have been coded with a medical dictionary that is different from the one being used in the database in which they are being migrated, are all factors that might alter signal detection results.

These caveats do not imply that statistical data mining methods are useless, but that they provide an incremental value to a pharmacovigilance system provided their potential gains and limitations are carefully assessed in the context of the characteristics of the data the organization needs to evaluate.

**Points to Consider for Implementing a Signal Detection Method**

To avoid buying expensive data mining tool software that may not be fully utilized if it is not fit for the organization’s needs, many operational and organizational aspects (of which the main ones are outlined in the table below), need to be considered.

**Signal Detection: Operational and Organizational Key Points**

<table>
<thead>
<tr>
<th>Guiding principles</th>
</tr>
</thead>
<tbody>
<tr>
<td>The organization should facilitate rapid informed communication and decision making in support of the pharmacovigilance unit</td>
</tr>
</tbody>
</table>

| Relevant staff should be trained on the tools and processes to optimize the detection of signals and their evaluation |
| Pharmacovigilance staff members should collaborate with experts from different disciplines according to the needs of the signal detection program |
| Signal detection activities should be performed in compliance with operating procedures and legal requirements |
A Signal has been Detected: What Comes Next?

Another aspect of the above-mentioned limitations is that the identification of a signal does not imply any causality between an event and a drug, but is only a starting point for further research and evaluation.

Since evaluating all signals in detail would consume huge resources, signals need to be prioritized. In other words, it needs to be established which signals need to be reviewed more expeditiously than others based on scientific and public health factors such as the strength of association, the level of evidence in the concerned cases that the adverse reaction is causally related to the drug of interest, the biological plausibility, the number of cases reported within a defined time frame and the adverse reaction health consequences. In addition, the population in which the adverse reaction is observed, attention from the media, risk perception by the general population and political obligations need to be considered.

Once signals have been prioritized, all the body of evidence which is immediately available should be evaluated: reports of adverse reactions consistent with the signs/symptoms or diagnosis under evaluation should be retrieved and analyzed together with other data sources such as preclinical studies, clinical trials, epidemiological studies, published literature, other databases containing pharmacovigilance data. The congruency or inconsistency of these data with the original signal should be assessed by a multidisciplinary team.

When the analysis of all the available data does reach a reasonable level of suspicion that an event is related to the drug or when the level of risk is not clear, further activities to characterize the risk (ie, to understand if it can be prevented, which is its seriousness, severity, reversibility, frequency of occurrence, public health consequences) can be considered.

The aim of all the described steps is to identify a proportionate course of action for signals/risks. That includes evaluating whether a signal should be reported to the Authorities, if and how it should be communicated to the patients and to the public and which risk minimization activities, if any, are needed.

Giovanni Furlan, PharmD is the Director of Pharmacovigilance Consulting and QPPV at PrimeVigilance. Readers can contact Giovanni at giovanni.furlan@primevigilance.com

The author would like to thank Dr Elliot G. Brown for his advice on the article contents and for reviewing it.
INTRODUCTION

Understanding the complete safety profile of a drug is dependent upon postmarketing surveillance and spontaneous reports of adverse events (AEs) from both consumers and health care providers. These occur after the drug is approved and begins to be used by a broader population of patients than those studied in the clinical development program. In 2009, the last full year for which data are available, the FDA reported receiving over 580,000 spontaneous AE reports from health care professionals and consumers. Fifty-five percent (55%) of these events were reported by health care providers and 47% by consumers. Ninety-four percent (94%) were reported to manufacturers or distributors who are required to report them to FDA. Of the cases reported to FDA, over 330,000 (67%) were serious and unlisted AE reports and, therefore, required a 15-day expedited report.

The vast majority of these spontaneous AE reports are made via phone directly to the manufacturers and distributors of drug products. The most critical component of the report is the ability of the contact center agent to interact and communicate with the reporter effectively during the call to uncover the full story of the AE so that it can be evaluated for medical significance.

WHERE ARE THESE EMBEDDED ADVERSE EVENTS (AEs)?

In reporting AEs, consumers and health care providers often do not differentiate an AE from a product complaint. Consumers often say, “I have a complaint about Product X: it caused a headache whenever I took it.” The consumer is really reporting an AE rather than a complaint. Similarly, the underlying reason for a medical product inquiry can be the occurrence of an AE: the health care provider may ask, “Does Product X cause headaches?” In this case, the health care provider may be asking the question relative to a patient who is experiencing the headache while taking Product X. In both of these cases, the AE is embedded within either the product complaint or the medical inquiry and must be uncovered during the conversation with the reporter in order to be documented and reported as required.

In a sampling of cases reported through a contact center, over 7,600 contacts from consumers and health care providers were made to manufacturers and distributors of various mature pharmaceutical products in several different therapeutic categories. These contacts generated 3,690 medical inquiries (MI), 748 AE reports and 3,697 product complaint reports (PC). In this sample, 486 (6.4%) of the cases included some combination of reasons for the contact (See Tables 1 and 2).

Of the total 748 AE reports, 415 (56%) were reported with either a MI (25%) or PC (26%) or, in 34 cases (5%) both an MI and PC. Only 333 (44%) of the AE reports gave the AE as the only reason for contact (See Figure 1). In these combination cases, discussion with the reporter uncovered the embedded AE which was, in many cases, the stimulus for the contact. Of these embedded AE reports, 10 (2.4%) were serious AEs: 7 within an MI and 3 within a PC. Of the 10 serious AE reports, 8 were received from consumers and 2 from physicians. Four of the 10 were assessed as serious and unexpected and, therefore, required a 15-day expedited report. All 4 were reported by consumers.

Table 1 - Contact Center Summary

<table>
<thead>
<tr>
<th>Contact Center Cases</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Contacts</td>
<td>7615</td>
<td></td>
</tr>
<tr>
<td>Contact Reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Inquiry (MI) Only</td>
<td>3400</td>
<td>44.6</td>
</tr>
<tr>
<td>Product Complaint (PC) Only</td>
<td>3396</td>
<td>44.6</td>
</tr>
<tr>
<td>Adverse Event (AE) Only</td>
<td>333</td>
<td>4.4</td>
</tr>
<tr>
<td>Cases with Multiple Reasons</td>
<td>486</td>
<td>6.4</td>
</tr>
<tr>
<td>Total</td>
<td>7615</td>
<td>100.0</td>
</tr>
</tbody>
</table>
is embedded with another type of case should be focused on the staff member who receives the initial contact and on procedures for review and processing of cases.

Contact Center Agents

Contact center agents (CC-Agents) who receive the initial contact from inquirers/reporters must be educated and trained to identify and process all types of cases. Registered nurses are well prepared through their clinical training to interview patients using a friendly, supportive and investigative style to elicit and document a complete medical history. Nurses learn to communicate with patients helping them to feel comfortable and, therefore, willing to share both solicited and unsolicited information. These skills and techniques are readily transferable from the health care setting to telephone interactions with patients who may be anxious and reluctant to share information with a person that they do not know.

Nurses are also trained during their clinical experience to communicate with a wide variety of health care providers consequently serving as patient advocates and liaisons between the patient and health care provider. These skills are also readily transferable to interviewing health care providers who are reporting an adverse event during the initial contact as well as initiating follow-up interactions with health care providers.

While the number of product complaints reported in combination with either an AE or MI is fewer than those for AEs, overall 8% of the PCs were reported in combinations. In this series of cases, 88% (172 of 196 AE-PC combination cases) were lack of drug effect reports typically characterized as lack of efficacy by consumers.

Uncovering embedded product quality complaints is also critically important since complaints alleged to include mislabeling, product contamination, significant chemical, physical or other change in the distributed drug product or any failure of distributed product to meet its specifications are potentially reportable to FDA by the manufacturer within 3 working days as an NDA – Field Alert Report. None of the PCs in this series were NDA – Field Alert reports.

Strategies to Uncover Embedded Adverse Events

Timely recognition and identification of embedded AE and product complaint reports become very important since both are related to the safe use of the drug product and are subject to regulatory reporting. The ability to uncover or identify either the AE or PC which

<table>
<thead>
<tr>
<th>Cases with Multiple Reasons</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE with PC</td>
<td>196</td>
<td>40.3</td>
</tr>
<tr>
<td>AE with MI</td>
<td>185</td>
<td>38.1</td>
</tr>
<tr>
<td>MI with PC</td>
<td>71</td>
<td>14.6</td>
</tr>
<tr>
<td>AE with PC and MI</td>
<td>34</td>
<td>7.0</td>
</tr>
<tr>
<td>Total</td>
<td>486</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2 - Embedded Combination Cases
care providers and a thorough understanding of AEs and PCs provides an ideal CC-Agent. These individuals are not only capable of uncovering an embedded AE or PC during the initial contact but, at the same time, they obtain all available information required for processing the reported events during the initial call. As a result, the need for follow up with either patients or health care providers is minimized and efficiency of case processing improved. While nurses are not the only health care professionals who can serve as CC-Agents, their unique combination of skills makes them ideal candidates for these positions.

Case Processing Procedures

Procedures should also be designed to ensure data quality, review each case for an embedded AE or PC, and maximize processing efficiency. Documentation of all available case information for each AE and/or PC during the initial call by one CC-Agent minimizes loss of information due to transfer of calls. Likewise, if the caller is transferred to a different agent for each type of report, the repetition of information increases the potential for discrepancies. Data capture in one electronic system that can be accessed by each group responsible for processing different types of cases further reduces the potential for error. Documentation of all available data for the entire case during the initial call minimizes the need for follow up, minimizes inconvenience to the reporter and improves efficiency of case processing.

Following receipt, documentation and data entry of case information, each case should be reviewed for an embedded AE or PC report. Peer review of case data including the AE and/or PC narrative is one very effective way to accomplish this and minimize the potential of overlooking the embedded event. This review should be timely in order to accommodate the strict reporting requirements for both AEs and Alert PCs required by the regulations. Training opportunities exist for the entire CC-Agent staff when the embedded AE or PC is not identified during documentation but is subsequently identified through peer review.

Table 3 - Strategies to Uncover Embedded Adverse Events

Conclusion

Adverse event and product complaint reports are often embedded within a case contact initially placed for a different reason. Since reports of both AEs and PCs are related to the safe use of pharmaceutical products, it is critical that embedded AEs and PCs be uncovered, documented and processed in a timely way so that regulatory reporting obligations are met. An experienced, well trained contact center staff and processing procedures designed to uncover these events are necessary to assure compliance with the regulations.

References


Contact Center Agents

- Clinical experience interviewing patients
- Experience communicating with health care professionals
- Regulatory training for AE and product complaint reporting

Case Processing

- All case information received and documented by one CC-Agent
- Data captured in one electronic system accessible by all groups
- Timely peer review of case data for embedded AE and/or PC

Carole DeRoche is the President of DDN Medical Affairs, A Dohmen Company. She can be reached at cderoche@ddnmedicalaffairs.com
The Importance of Proper Training in Terminologies for Quality Coding and Its Impact on Data Analysis

Samina Qureshi

Introduction
Pharmacovigilance and the capture of data in the health care/life sciences context involves the use of many diverse terminologies. The purpose of these many terminologies is varied, ranging from capturing adverse events to categorizing diagnoses and procedures. The most important use of these terminologies involves the performance of good quality coding. Employing high quality and superior standards of coding translates into choosing terms within the respective terminology that most closely and accurately captures the concept observed or captured. Whether that concept is a product name in the case of pharmaceuticals or expression of an adverse event, the principle objective remains the same: maintaining the integrity of information. The key to achieving this objective successfully is the proper training of individuals performing coding tasks. Only through high-quality training can observers ensure that the end result is objectively correct, good data is captured, and reflect the precise phenomenon or incidents observed in the source documentation/records.

The primary purpose of developing coding terminologies is to provide a uniform, consistent and reliable methodology to express concepts without losing expression of the integrity of the event. The correct use of coding terminology is accomplished only through proper training. Such training, in turn, allows for the capture of “good” data and the production of aggregate results that lend themselves to reliable and meaningful analysis. Such a process ensures accurate signal detection that is neither diluted nor magnified.

Because there are numerous terminologies, this article focuses on those described in the Medical Dictionary for Regulatory Activities (MedDRA) which is often used to capture adverse events after drug exposure, and the World Health Organization’s Drug Dictionary (WHO-DD) which is used to capture concomitant medications often used in pharmacovigilance. The article also references the International Classification of Diseases (ninth revision) which is primarily utilized to capture diagnoses and procedures in health care settings for reimbursement and for statistical data analysis purposes, such as epidemiological analysis or trending of disease incidence.

Important Elements of an Effective Training Program
The effectiveness of any terminology depends upon (1) the extent to which it precisely captures the observed event or concept, and (2) the extent to which it relays to the end-user its purpose and structure of this observed event or concept. Thus, consistent understanding and interpretation of terminologies is critical for both the coders who perform the initial capture and assign particular terms/codes to observed phenomenon, as well as data analysts and statisticians who perform analysis on aggregated coded data.

A well developed training course or program on terminologies should remain mindful of these twin measures of effectiveness by providing contextual perspective and background on the purpose of the relevant terminology, as well as some historical details on its development. For MedDRA and WHO-DD, these terminologies developed, in part, as a result of the wide-spread use of Thalidomide as a sedative in Europe from 1957-1961. The resulting teratogenicity spurred the immediate demand for a centralized reporting system and the use of common standardized terminologies across incidents. Providing this contextual...
explanation for the development of the relevant terminologies allows users to realize the importance and relevance of their coding task to the larger pharmacovigilance framework. In particular, such context allows users to better understand how their coding choices relay concepts which are utilized to convey potential signals. Within the larger pharmacovigilance framework, the use of appropriate and standardized terminologies contributes to public health, safety and welfare.

In addition to developmental context, training programs should provide an in-depth understanding of the structure and/or hierarchy of the relevant terminology. For example, in providing training on MedDRA, users should understand the five hierarchies ranging from the broadest System Organ Class (SOC) to the most granular level of Lowest Level term (LLT). In the WHO-DD context, the relevant structure/hierarchy ranges from discussions of drug code significance and its components, as well as an overview of the integrated Anatomical Therapeutic Chemical Classification. The coder should have sufficient training and education to comprehend this structure/hierarchy and the concepts that the terminology addresses within this structure. For MedDRA, coded terms at the Preferred Term level are each unique medical concepts. Accordingly, an educational background which provides an intimate familiarity with clinical concepts (medicine, nursing, or pharmacology, for example) would provide sufficient context for the proper coding. Similarly, for WHO-DD, an educational background in the health care/life sciences is ideal for users utilizing this terminology. Not only is the right educational background critical, but so is the need to stay current within the requisite discipline. For example, until recently, familiarity with basic medical terminology and knowledge of basic health science fundamentals in pathology and physiology was sufficient for ICD-9 coding. Recently however, Centers for Medicare & Medicaid Services (CMS) mandated the adoption of ICD-10 by October 2013. Thus, the background previously adequate for ICD-9 is no longer enough for those who must perform ICD-10 coding. The new version ICD-10 code sets are much more granular and include greater detail, changes in terminology, and expanded concepts for injuries, laterality, and other related factors. This increased level of detail conveyed in the ICD-10 codes is evident from the sheer growth in number of ICD codes - the codes increased from 17,000 in ICD-9 to over 155,000 ICD-10. This expansion requires greater knowledge in anatomy, physiology, pathophysiology, and pharmacology. As the development of ICD-10 coding highlights, proper training of coding staff is essential for effective performance.

The dangers of an inadequate background or education in the required subjects are obvious: results are likely inaccurate and coding is likely not meaningful. Strong and relevant education will also lead to an appreciation of the importance of coding uniformity and consistency within and across coders. If the same adverse event is coded differently in MedDRA by multiple coders or by the same coder in each case report, results will translate into the occurrence of different medical concepts. Such a result will skew the analysis and dilute the frequency of the event occurrence; thereby potentially leading to missed signals.

The need for training is typically required at the coder level but it is also necessary for analysts, statisticians, researchers, and others who rely on aggregated coded data to understand the nature of the relevant terminology and an appreciation of the precise concepts/events captured by particular codes. In the case of WHO-DD, understanding the significance of the eleven digit drug code and its components — drug record number (first six digits), sequence 1 (next 2 digits) and sequence 2 (last 3 digits) — allows the analysts to utilize the records fully and perform meaningful analysis. If properly trained, an analyst would understand that the drug record number is common for all entries containing the same active ingredient or unique combination of active ingredients. The analyst would also understand that sequence 1 identifies the salt or the ester of the active ingredient in a single ingredient product. Sequence number 2 (seq 2) identifies trade names and in some cases a synonym to a generic name. The entry with seq 2 value 001 identifies the name of the generic drug record number level, the preferred name. In single ingredient drug record numbers this will also be the substance name. For multiple ingredient drug record numbers it will be the trade name of the first product with that combination of ingredients. Understanding these detailed concepts so the analyst does not dilute or over-represent a signal in conducting research and preparing final analyses is vital.

Proper training in any coding terminology also requires familiarity with coding guidelines that provide an overview of the organization’s purpose and environment. These coding guidelines often offer insight of best practices from the
perspective of the maintenance organization with responsibility for the terminology, detailing that organization’s interpretation of specialized “rules of the road” within its own unique environment. In the case of MedDRA, this perspective is offered by the International Conference on Harmonisation (ICH) which endorsed MedDRA’s “Term Selection: Points to Consider” document. Ideally, training should provide education on the relevant organization’s specific guidelines, taking into account each coding principle reflected in the Best Practices guide and illustrating through examples the best method to code for their staff. Documenting these examples and revising them, if appropriate, will ensure consistent, uniform and accurate coding by the coding staff. The need and importance of coding guidelines is particularly important in times of safety audits. Questions related to “soft” or improper coding often arise in these audits, and a well documented methodology can help address these questions by showing consistency and uniformity in the application of governing principle.

Formal training should also include a clear understanding of Best Practices and how individual organizations interpret each principle codified in these practices. Trainers should provide the coder with “hands-on” exercises of varying levels of difficulty. These exercises should resemble the type and nature of data that the coder will address in live production.

Other Training Considerations to Ensure Effectiveness

As learning preferences vary from individual to individual and from trainer to trainer, organizations should strive to utilize a combination of learning styles when conveying educational concepts. Such diversity in approach will ensure that trainers stay connected with the audience. In addition, each trainer should seek to employ sensory, visual, verbal or intuitive styles in various combinations during training. Ideally, training will involve a combination of techniques to make the training interesting and effective for an audience with different learning styles. Training should also employ processes that allow for interaction between the coding trainee (protégé) and coding mentor (trainer) to facilitate feedback on questions and challenges faced.

Often due to financial restrictions, some organizations adopt a casual attitude towards training of their coding staff. Typically, such organizations conduct “training” by having untrained or new staff simply shadow more senior coding staff. This tactic may work in some rare instances, but even the best coding staff may not always have the teaching aptitude or patience required for such training. Without a precise methodology consisting of the principles discussed above, proper and effective learning is difficult. Other organizations have developed their own training curricula to provide training for coding staff. If such a curriculum is well organized and incorporates terminology versioning updates, it may also work. However, without the formality of a training session, learning from manuals is often ineffective, and written guides are often unable to address the myriad of questions that arise during the training of coding staff.

Because of the importance of “live” questions and answers, the individuals who conduct the training should be subject matter experts in the terminology they are teaching. Such expertise allows individuals who are learning, to obtain proper technical feedback to challenging and technical coding questions. Individuals who are professional trainers but not experts or users themselves in the terminology should not teach technical topics such as coding.

One factor often overlooked during training involves an introduction to the tools provided to perform the coding. In case of MedDRA and WHO-DD, it is important to train coding staff in the proper use of the browsers that will allow optimal, user-friendly searching. Ideally, training should utilize the same browser that the coding staff will use in the work environment. Proper knowledge with the proper use of good tools will allow for optimal performance.

Once formal training in a terminology is completed, training should then demonstrate specific application of the concepts within the organization, remaining mindful of organization-specific guidelines. Trainers may measure knowledge of these concepts through the use of testing metrics in place to assess performance of the coders’ post-formal training. Trainers should consider developing processes for remediation and relearning if testing metrics reveal any areas of weakness. Indeed, organizations must routinely assess and perform quality control on coding work to maintain uniformity in standards and to determine if the organization’s guidelines and standard operating procedures are implemented properly. New version releases of terminologies (bi-annually in the case of MedDRA and quarterly in the case of WHO-DD) highlight the important need for periodic assessments of coding performance. Often in larger organizations, post—
version release meetings are held to discuss changes to terminologies and the concomitant need for new guidelines. The feedback from coding staff often drives changes or updates in an organization’s internal guidelines on coding terminologies.

**Conclusion**

Good data analysis requires that terms captured in aggregated data are precise and true reflections of the concept observed or relayed in the source. Over-coding the same concept terms will result in magnification of a signal, and under-coding of a term will result in dilution of a signal. Accordingly, it is vital that coding maintain the true integrity of observed concepts through the use of appropriate terminology. Achieving this objective in coding depends on proper, robust, and in-depth training of coding staff. Such training should include organization-specific coding guidelines that allow the coder to incorporate the concepts learned to their organization’s specific environment. The mentors providing the training should also be experts in terminology and have demonstrated aptitude in teaching. Good data going into a system will result in true signal detection in analytical outputs. Through proper training, coding staff can avoid the maxim “garbage in, garbage out,” and instead, allow them to ensure that “good data in results in good data out.”

Samina Qureshi, MD, is Manager, Drug Safety Surveillance, at PSI INTERNATIONAL, Inc, in Rockville, MD. You can contact her at squreshi@psiint.com

---

**The New England IRB Advantage**

New England IRB is the premiere AAHRPP-accredited, central IRB, providing quality study review services in the United States, Canada and Mexico.

**Quality**
- Full AAHRPP accreditation
- In good standing with FDA
- Multi-tiered QA process

**Review Timelines**
- One-week protocol review turnaround
- 24-hr site review

**FastTrack™ Web Portal**
- Submit documents directly for review
- 24/7 secure access

**Customer Service and Flexibility**
- Single point of contact on dedicated client study team
- FREE Protocol Consultation
- Pre-submission kick-off meeting

Contact us to discuss your next study:
New England IRB 85 Wells Ave, Newton, MA 02459
www.neirb.com info@neirb.com 617-243-3924
The Developmental Safety Update Report
The New Way to Drug Safety or a Born-again Old Report?

Giovanni Furlan and Steve Douglas

Annual Safety Reports Limitations
About five years ago, my boss asked me to prepare my first Annual Safety Report (ASR) and repeatedly advised me to prepare a template before starting to draft the report, suggesting that otherwise, it would have been very difficult for me to write the report. In fact, the European regulations only provided very broad guidance on the structure and format of this document and of the three pages of the EU Commission Guidance dedicated to ASRs, less than one page is dedicated to the real scope of this document: the analysis of new findings related to the IMP, to clinical trial conduct and an explanation of which new risk minimization measures might be necessary. All the other pages were dedicated to the structure and content of line listings, summary tabulations, and how to calculate the document reporting time frame.

The ASR template I prepared followed, as much as possible, the ICH E2C template for Periodic Update Reports (PSURs) for marketed drugs. My first ASR was on a drug that had just entered phase 3 study. Since exposure in humans was inevitably limited, the introductory part was largely dedicated to the drug mechanism of action in order to extrapolate the basis and rationale for the theoretical risks human beings could have experienced when taking the drug.

The Authority assessment of the ASR introductory part was not very encouraging: they wrote that the scope of the report was only to describe the adverse reactions that had actually occurred and no hypothesis or explanations based on pharmacology were needed.

Interestingly, in 2008 the European Commission stated that since PSURs were too often only line listings of adverse reactions, the new directive 2001/83/EC would amend these reports to make them an analysis of the benefit-risk balance of the drug. It can be easily imagined that, if the PSUR, a structured document with specific sections dedicated to the analysis of the drugs' evolving safety profile, had not reached its full objective, then the ASR, a non-structured document whose contents are described by a few pages focusing on line listing and summary tabulations, had in most instances completely missed the aim of detecting and analyzing the Investigational Medicinal Product newly emerging risks.

In the US, annual reports for Investigational New Drug applications (INDs) have been used for describing the evolving knowledge of the Investigational Medicinal Product since many years before ASRs. This document mostly contains lists and summaries: a critical summary of the drug evolving safety profile is not explicitly required. Furthermore, the content of an IND annual report is very different from that of an ASR; therefore, an IND annual report would not have been accepted by European regulators and, vice versa, an ASR would not have been accepted by the Food and Drug Administration (FDA).

Reasons for a New Annual Report: Rationalizing Resources and Science
The International Conference on Harmonization (ICH) E2F guideline on Development Safety Update Reports was finalized in August 2010 with the aim of providing “a common standard for periodic reporting on drugs under development among the ICH regions” so that the same document can be submitted to all regulators, thereby rationalizing the use of resources.

The real change brought by the DSUR, however, regards the approach to drug safety: if the ASR was intended to be a concise description of the new safety information and an assessment of the status of patients safety, the DSUR is a “thoughtful review and evaluation of pertinent safety information collected during the reporting period” to “ensure that sponsors are adequately monitoring and evaluating the safety profile of the investigational drug.” The main aim of the DSUR is, therefore, to avoid uncritical lists of individual

SS1-DUSR.indd 37
7/28/11 9:49 AM
case reports or of studies, such as the ones that have led the EU Commission to change the PSUR scope. In fact, one of the most important sections of the DSUR, the Overall Safety Assessment, should be a concise, integrated evaluation of all new relevant clinical, nonclinical and epidemiological information obtained during the reporting period evaluated in the light of cumulative drug knowledge.

What would happen today if I wrote the DSUR with the same approach as my first ASR, when I was trying to understand which would be the adverse reactions in humans due to the drug mechanism under review?  Good news for me: I would probably not be rebuked. In fact, both ICH E2F and the CIOMS DSUR guideline report an example of how to write the section “Summary of Important Risks” for a fictitious drug. They imagine this drug has been associated with syncope in some patients and state the causal relationship strengthened by the drug having nitric oxide vasodilator properties that provide a mechanistic explanation for the reported adverse reaction.

**DSUR Structure and Content**

The DSUR aim and scope is clearly a step forward towards a scientific approach to drug safety, but what about its structure and contents: do they assist a scientific approach to pharmacovigilance?

Let us quickly look at the DSUR structure whose chapters can be grouped into three types:

- **Those summarizing and presenting cumulative information or information collected during the reference period.** Within this group of chapters we can probably include those on worldwide marketing authorization status (if applicable), the actions taken during the reference period for safety reasons, changes to the reference safety information, inventory of the ongoing clinical and completed clinical trials, presentation of the line listings and summary tabulation, and patient exposure.

Even with some differences when compared to the ASR or the PSUR, these chapters are not so different from what has been prepared until now for these documents. Furthermore, the information required by chapters on patient exposure closely resembles how this information is presented in the Risk Management Plan (RMP) Safety Specification section.

- **Those summarizing clinically important safety information collected during the reference period.** Until now companies have been presenting the most important individual case safety reports and articles. With the DSUR, individual cases will not be presented: a short narrative or a synopsis of information representing a new safety signal supporting or refuting a previously identified safety issue is presented. This information includes safety findings from completed and ongoing clinical trials, noninterventional studies, marketing experience, nonclinical data, literature, etc. Furthermore, once a study is completed or literature screening is performed, a succinct critical evaluation of the safety results will need to be prepared in order to include it in the DSUR.

Since these chapters are so different from similar sections that have been prepared until now, to prepare them in line with expectations, drug safety departments might have to change their operations and, maybe their structure.

- **Those providing an integrated critical summary and analysis of the safety information received during the reference period plus cumulative data.**

These chapters split the contents of PSUR section, “Overall Evaluation,” into three parts: the presentation of the safety issues identified during the reference period, the presentation of the benefit-risk considerations, and, the cumulative summary of the important risks. This last chapter is very similar to the Risk Management plan sections on adverse events/adverse reactions and interactions.

**A New Document That Already Needs to be Improved?**

In the current environment of resource constraint within the pharmaceutical industry, key factors towards a scientific approach to pharmacovigilance should ideally avoid unnecessary overlap and redundancy so that resources are optimized for protecting patient safety.

From this point of view, the very first pages of the DSUR are not particularly encouraging. The DSUR overlaps with the PSUR. Therefore, once a drug has been authorized and clinical trials are still being conducted, the data lock of the PSUR can be aligned to that of the DSUR, and since both of these documents must be prepared within 60 days, it is easy to imagine already stretched drug safety departments engaging in “copy and paste” exercises. Furthermore, since the summary of the safety findings from marketing experience need to be summarized in DSUR Chapter 11, it is reasonable to forecast that many organizations might shorten the timelines for preparing the PSUR in order to include a summary of (or just copy and paste) “Overall Evaluation Section” or “Conclusions” of the PSUR in the DSUR.
A similar copy-and-paste exercise might also be used in some sections of the Risk Management Plan.

The aim of providing one identical document to all authorities to avoid unnecessary bureaucratic exercises does not appear to have been completely achieved. In the DSUR, there is a specific chapter where specific information requested by single authorities is required.

Partial document redundancy and the maintenance of local requirements have contributed to expand the DSUR to a 20-chapter document (twice the number of chapters contained in PSUR). The preparation of such a complicated document will inevitably present a further burden on already stretched drug safety departments. Careful planning will be required regarding the preparation of the DSUR in order to avoid unnecessary duplication of effort. The following table provides an example of the activities that need to be planned and the caveats to be considered during DSUR preparation. However, it should be noted that activities and caveats change according to the product developmental stage. If the Investigational Medicinal Product is in premarketing stage only and has not been authorized yet, the actions and caveats regarding PSURs will not be applicable. This also applies to the Risk Management Plan: this document will need to be prepared in time for the marketing authorization application, even if it is advisable to prepare it during the first drug development stages.

To conclude, the DSUR is a significant step forward towards a scientific approach to drug safety but, as recognized by the final concept paper for the new PSUR, overlap between regulatory documents remains to be significantly improved as do the challenges presented by regional differences. These factors contribute to making the DSUR a complex document; complexity does not necessarily lead to better quality, but often causes mistakes and misunderstandings.

### DSUR Planning

<table>
<thead>
<tr>
<th>DSUR section</th>
<th>Action</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide Marketing Authorization Status</td>
<td>Ensure consistency with the PSUR.</td>
<td>A narrative, not a table is required.</td>
</tr>
<tr>
<td>Actions taken in the reporting period for safety reasons</td>
<td>• Collect data from clinical trials and post marketing.</td>
<td>The section only includes actions taken during the reference period, with the exception of the list of regulatory requests limiting the development of the Investigational Medicinal Product (IMP) which is cumulative.</td>
</tr>
<tr>
<td></td>
<td>• Include risk minimization activities for both clinical trials and post marketing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ensure the reported information is consistent with that reported in the PSUR (sections “Update of actions taken ...for safety reasons”) and Risk Management Plan (risk minimization activities section)</td>
<td></td>
</tr>
<tr>
<td>Changes to reference safety information</td>
<td>The Investigator’s Brochure (IB) is updated once a year. Perform signal detection and IB updating just before DSUR Data Lock Point: it will help the preparation of sections where safety findings are presented and discussed.</td>
<td>Whenever the reference safety information is not the Summary of Product Characteristics or the Core Safety Information, expectedness should not performed versus the list of all the Serious Adverse Events (SAEs) included in the IB. Prepare a list of adverse reactions for which there is enough evidence to reasonably suspect they were caused by the IMP. This is the list to be used for expectedness call.</td>
</tr>
<tr>
<td>Inventory of clinical trials or completed during the reporting period</td>
<td>Consider whether clinical trials need to be presented in separate tables divided by indication, formulation and/or study population.</td>
<td>The safety results of studies conducted with different formulations, indications, and populations might differ.</td>
</tr>
<tr>
<td>DSUR section</td>
<td>Action</td>
<td>Caveat</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Estimated cumulative exposure</td>
<td>• Collect data from clinical trials and post marketing experience.</td>
<td>• Patient exposure does not only regard the reference period (as does the PSUR), but is cumulative.</td>
</tr>
<tr>
<td></td>
<td>• Collect data per age, sex, race.</td>
<td>• Maintain consistent methodology for calculating patient exposure between post marketing (and PSUR) and clinical trial data.</td>
</tr>
<tr>
<td></td>
<td>• For blinded clinical trials estimate patient exposure according to the proportion of patients enrolled in each treatment arm, as per protocol.</td>
<td>• Ensure consistency with clinical trial presentation and SAE summary tabulations: if clinical trials and summary tabulations are presented by indication or formulation, present patient exposure in the same way.</td>
</tr>
<tr>
<td></td>
<td>• Patient exposure does not only regard the reference period (as does the PSUR), but is cumulative.</td>
<td>• In the PSUR, patient exposure is required to be calculated for the reference period. It is suggested to add cumulative exposure to the PSUR so to be consistent with the DSUR.</td>
</tr>
</tbody>
</table>

| Line listings and summary tabulations             | • Prepare line listings for the serious adverse reactions which occurred during the reference period. | Review the cumulative summary tabulation of Serious Adverse Events (SAE) with care: the analysis of aggregate data is more important than causality assessment of a single case report. |
|                                                  | • Prepare cumulative (starting from the date the first IMP clinical trial was authorized) summary tabulation for Serious Adverse Events (not reactions). |                                                                                                                     |
|                                                  | • Evaluate the variables by which data need to be presented (e.g., indication, dosage, route of administration). |                                                                                                                     |

<p>| Significant findings from studies during the reporting period** | • For each completed study, prepare a brief analysis of the safety findings that confirm or disprove previously identified safety issues. | • Remember to classify studies in clinical trials, non-interventional studies, meta-analysis, investigator initiated studies, studies conducted by a co-development partner, and non-clinical studies. Each study type is included in a specific chapter according to its classification. |
|                                                               | • As for other sections (e.g., safety findings from marketing experience, literature) present the information whose meaning will be interpreted in DSUR section,”Overall Safety Assessment”. | • Do not present single case reports, but a critical summary of the study safety findings |
|                                                               | • If the DSUR is for a drug that is also developed as a combination therapy, collect results of studies conducted with the combination therapy. |                                                                                                                     |</p>
<table>
<thead>
<tr>
<th>DSUR section</th>
<th>Action</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety findings from marketing experience</td>
<td>Ensure PSUR section “Overall Evaluation” is prepared in time (if PSUR and DSUR data lock points are aligned).</td>
<td>If the PSUR “Overall Evaluation” section is a long one, prepare a brief summary of the key safety findings.</td>
</tr>
</tbody>
</table>
| Literature                                       | • Select the articles that highlight new findings or that add new information (positive or negative) to already known potential or identified risks.  
• Classify the articles by safety topic.          | Do not present summaries of single articles.                            |
| Region-specific information                      | Prepare a brief analysis of the impact the safety information of each topic required by local regulations has on the product safety profile.  
Discuss the safety findings presented for each topic in section “Overall Evaluation”. | • Obtain information on local DSUR requirements in time: ICH2F and European Medicines Agency DSUR guideline only provide examples of which additional information might be required.  
• The safety information in this section might be redundant with that reported in other sections (e.g., safety issues highlighted from the list of subjects who died during the reporting period might have already been reported in section “Significant Findings from Clinical Trials during the Reporting Period.”) |
| Overall safety assessment                        | • Prepare a concise evaluation of all safety information contained in previous DSUR sections.  
• Prepare the PSUR in time so that new safety information discussed in this DSUR section is also reported in the PSUR.  
• As for PSUR section, “Overall Evaluation”, prepare separate subsections for all the points ICH E2F section 18.1 requires to discuss.  
• Ensure all safety information for all the points listed in ICH E2F section 18.1 is collected from all DSUR sources. | • This section is only for the safety information originated during the DSUR reference period, but the impact this information has on the already known risks needs to be discussed in the context of the cumulative knowledge of the safety issue.  
• Maintain consistency with other DSUR sections: if the SAEs summary tabulations, studies and safety issues presented in previous sections have been organized by indication, dosage or formulation maintain the same structure.  
• For safety issues for which new information has been received, there will be an overlap with DSUR section “Summary of important risks”.  
• “Benefit-Risk Considerations” should not be limited to the statement “The benefit-risk profile of the drug has not changed”. For each indication, prepare a concise summary of the main benefits and risks and a statement on product benefit-risk balance. (Refer to CIOMS VII, page 132-134 for examples). |
Summary of important risks

Present a cumulative summary of all the important identified and potential risks (i.e., those that might impact on the product benefit-risk balance) regardless of whether new information was retrieved during the reference period.

This section overlaps with the Risk Management Plan "Safety Specification" part, but the format is different.

Ensure consistency with the RMP: significant new safety findings might need to be added to the RMP. New information on potential or identified risks already reported in the RMP might be identified. Discuss this information in the DSUR and consider the possibility of updating the RMP.

Conclusions

Ensure the actions taken to address emerging safety issues are consistent with those reported in RMP "Pharmacovigilance plan" and "Risk Minimization" sections.

References

3. Code of Federal Regulations, Title 21. part 312.33

* Not all DSUR sections are presented in the table.
** Includes DSUR sections: “Significant Findings from Clinical Trials during Reporting Period,” “Safety Findings from Non-Interventional Studies,” “Other Clinical Trial/Study Safety Information,” “Nonclinical Data.”

Giovanni Furlan, PharmD, is the Director of Pharmacovigilance Consulting and QPPV at PrimeVigilance. He may be reached at giovanni.furlan@primevigilance.com.

Steve Douglas, BS, is the Director, SGD Consulting and PrimeVigilance.
Effectiveness of REMS Tools

Sally Van Doren and James Buchanan

Introduction
In 2007, the Food and Drug Administration Amendments Act (FDAAA) was signed into law authorizing the Food and Drug Administration (FDA) to require a Risk Evaluation and Mitigation Strategy (REMS) from drug manufacturers, if deemed necessary to ensure that the potential benefits of a drug outweigh its risks. At the time of this writing, there have been 185 REMS approved by the FDA. Questions have been raised about the effectiveness of risk mitigation tools, as well as the methods used to evaluate them. The objective of this article is to discuss and present information on which REMS elements have influenced prescriber and patient behaviors leading to reduced product risks in patients.

REMS Components
- Goals
- REMS Elements
  2. Communication Plan
  3. Elements to Assure Safe Use (ETASU)

REMS Requirements
The FDA determines on a case-by-case basis which REMS components a manufacturer is required to submit. To help manufacturers develop their REMS, the FDA issued guidance for industry in September 2009 that provides the FDA’s current thinking on the format and content that industry should use for submissions of proposed REMS.

<table>
<thead>
<tr>
<th>Component/Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedGuide</td>
<td>A document written for the patient containing information on how to safely use a drug product.</td>
</tr>
<tr>
<td>Communication Plan</td>
<td>A description of the manufacturer’s plan to educate health care professionals on the safe use of a product to support implementation of the REMS.</td>
</tr>
<tr>
<td>ETASU</td>
<td>A description of controls required to mitigate a serious risk, such as physician or pharmacy certification, specialty distribution, or a patient registry.</td>
</tr>
<tr>
<td>Implementation System</td>
<td>A description of how ETASUs will be implemented.</td>
</tr>
<tr>
<td>Timetable for Submission of Assessments</td>
<td>The frequency of assessing REMS performance in achieving its goal. Unless otherwise specified the FDA expects assessments at 18 months, 3 years, and 7 years. This timetable is agreed upon upfront by the FDA and the manufacturer. This element is required for all REMS.</td>
</tr>
</tbody>
</table>
All REMS require manufacturers to provide answers to the following questions as part of the timetable for submission of assessments component:

- Is the program effective in mitigating the identified risk(s)?
- Are the communications in the program conveying a clear safety message?
- Has the program helped to prevent patients from being exposed to the identified risk(s)?

At present, the FDA is working on a draft guidance that in some cases would separate MedGuides from the REMS program, effectively removing drugs requiring them (which are typically less risky) from having to satisfy the more restrictive REMS requirements.3

Assessment of Potential REMS Elements
Let’s start by showing the usage breakdown for each REMS element among the currently approved REMS.

Of the current approved REMS
- 99% are using MedGuides
- 65% are using only a MedGuide
- 26% are using a communication plan
- 12% are using ETASUs, with 82% of those also using an implementation system
- 3% are using all three (MedGuides, a communication plan, ETASUs)

MedGuides
In 1998, the FDA established a program requiring the distribution of medication guides for drugs considered to pose a serious health risk, well before it was considered as a REMS tool post-FDAAA in 2007.

In 2007, the FDA held a public hearing announcing the results of a national survey of pharmacists that indicated low pharmacy compliance in regards to MedGuides. The results showed 70% of respondents were familiar with the term MedGuide, but only 20% knew that they were required for all prescriptions. Only 30% felt MedGuides effectively communicated risks, indicating that there is common confusion among pharmacists in regards to the definition, content, and requirements of MedGuides.4

Overall Assessment of MedGuides
- Too long and complex for patients to comprehend – discourages patients from reading them, and those who do may not fully understand them
- Unbalanced in the coverage of risks and benefits – emphasis towards risks
- Pharmacies are charged with distributing materials to patients – adds burden and cost for them
- Paper only communication for patients

As much as MedGuides have been used, published studies evaluating them don’t show much support for their use alone as an intervention in mitigating product risks.5 The FDA Director of the Center for Drug Evaluation and Research (CDER), Janet Woodcock, previously said, “The FDA has considered switching to a universal patient leaflet to replace MedGuides as part of REMS because the guides don’t effectively protect patients from medication errors and serious adverse events.”6 Even the FDA itself doesn’t think that MedGuides are working as intended.

Communication Plans
Dear Doctor Letters (DDLs) and Dear Healthcare Provider Letters (DHCPLs) are examples of communication plan tools. These tools are used to inform physicians and other health care providers of known or potential risks for new and existing drugs, including information regarding potential conflicts with other drugs.

Communication plans may include
- sending letters to health care providers
- dispensing information about REMS elements to health care providers to encourage implementation, explain safety techniques, or communicate serious risks of the drug to assure safe use

Based on a literature review of DDL and DHCPLs, the overall assessment is that they are often ineffective in changing prescribing behaviors, and similar to MedGuides, are generally ineffective in communicating risks when used as the sole risk communication tool.5

In 2005, a study was conducted that showed DDLs were distributed due to warning label changes only 26% of the time. They were most likely to be sent when the warning change included information about patients who shouldn’t receive the drug or would be at increased risk, or when the change involved a black box warning. According to this study, the biggest issue with the DDLs was that the most important information wasn’t easily apparent, often obscured by less critical information.
The study also found that most DDLs didn’t clearly present the critical information reducing their effectiveness to influence a change in physician prescribing behavior.7

In 2004, a study was carried out to assess the effectiveness of DHCPLs in changing prescribing behavior by evaluating contraindicated co-prescribing of tramadol and antidepressants. Before a DHCPL was issued, 22% of tramadol recipients were prescribed a contraindicated antidepressant. After the DHCPL was distributed, 19% were co-prescribed an antidepressant, a decline of only a 3%.8

These, along with other published studies, demonstrate a lack of effectiveness in changing prescribing behavior using provider mailings. In addition, since FDAAA requires that FDA assume responsibility for Communication Plans once a product goes generic, there already is less emphasis on the use of Communication Plans in REMS programs.

Elements to Assure Safe Use(s) (ETASUs)

ETASUs are the most restrictive REMS component. ETASUs require manufacturers to include goals to mitigate a specific serious risk listed in the labeling of the drug and that

- the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results
- each patient using the drug be subject to certain monitoring, or
- each patient using the drug to be enrolled in a registry

In some cases an implementation system may also be required for an ETASU drug; manufacturers must monitor and evaluate ETASU compliance, and outline steps to improve the REMS implementation.

The overall assessment of ETASUs is that, although they appear to control the distribution of drugs with known serious risks, they have been perceived by some stakeholders as an encumbrance to all entities involved throughout the supply chain. Some stakeholder comments have stated that ETASUs

- create a burden for all involved (eg, physicians, pharmacists, patients, manufacturers)
- distribution of drug is limited to only certain registered pharmacies or specialty pharmacies, which limits patient access (potential for preferential treatment by drug companies)
- may potentially introduce costs that outweigh the benefits of the drug

One of the earliest REMS programs with ETASUs was developed for thalidomide, a known teratogen. The REMS required registering all patients, pharmacists, and physicians in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S) risk management program that works to prevent pregnancies by requiring patients to use birth control while taking the drug. A similar risk management program, RevAssist, was developed for lenalidomide, an analog of thalidomide. These programs appear to be successful in minimizing the risk of pregnancy during drug use and thus birth defects.9,10

REMS Assessments

According to the FDA guidance, REMS assessments should include an evaluation of the extent to which each of the REMS elements are meeting the goals and objectives of the REMS, and whether or not the goals, objectives, or REMS elements should be modified. While this would appear to address the objective to evaluate the extent to which the program mitigates product risks, in practice the assessments tend to measure administrative details rather than actual safety outcomes. Types of assessments given as examples in the Guidance include

- survey to evaluate knowledge of a labeled serious adverse event (SAE) to determine whether patients are using the product correctly to prevent the adverse event (AE)
- evaluate use of the product as labeled
- survey of patients’ understanding of the serious risks of the drug
- report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- report on failures to adhere to distribution and dispensing requirements, and 843 corrective actions taken to address noncompliance

Vol 3 Issue 4 Global Forum
The results of these types of assessments may be useful from the standpoint of identifying weaknesses in the underpinnings of an educational program, but they do not directly address the purported purpose of the REMS – reducing product risk. In informal conversations with FDA staff members, the FDA recognizes this limitation and will be addressing it in the future. Perhaps as evidence of this is the newly issued guidance for class wide opioid REMS. In this guidance released April 2011, proposed assessments include a surveillance plan that includes monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics. Surveillance needs to include information on changes in abuse, misuse, overdose addiction, and death for different risk groups (eg, teens, chronic abusers) and different settings (eg, emergency rooms, addiction treatment centers, poison control call centers).

However, until assessments routinely include a measure of safety outcomes, it will be difficult to evaluate the extent to which REMS programs benefit the public health.

Survey of Stakeholders Regarding REMS Programs
A recent survey of stakeholders regarding REMS programs was performed by the Tufts Center for the Study of Drug Development (CSDD) in 2010. This study interviewed a select group of payers, pharmacists, health care providers, patient advocates, and biopharmaceutical companies with knowledge, experience, and interest in REMS programs. Their findings showed a general agreement (86%) among the respondents that information contained in REMS communications under the current guidelines wasn’t balanced between risks and benefits with more of an emphasis on the risks. There was a 75% agreement that the current REMS program needs to be fixed, and 79% of those surveyed thought the REMS program is worse than previous FDA risk management programs.

Another recent survey conducted in 2010 by the National Comprehensive Cancer Network (NCCN) interviewed a work group of physicians, pharmacists, nurses, hospital administrators, patient advocates, biopharmaceutical companies, and government employees with roles in the management of cancer patients subjected to chemotherapy. Their findings showed half of the respondents (52%) were somewhat or not at all familiar with REMS, with 74% of pharmacists the most familiar. When asked if they felt REMS were achieving their intended goal of better informing patients about drug safety risks, 61% agreed, while 60% believed that REMS will drive use toward drugs without REMS.

Conclusion
Risk management is increasingly becoming a critical component in the American pharmaceutical sector. Although many hurdles exist for drug manufacturers to get their drugs to the market, such as cost, complexity and coordination, the REMS program has actually helped approve some drugs that would otherwise not have been due to their risks.

Currently, MedGuides are the most common component included in REMS; however, it appears the FDA is planning to separate MedGuides from the REMS program, thereby reserving the more restrictive REMS requirements for drugs they consider risky. Patient and Physician/HCP surveys are commonly utilized in assessing knowledge, attitudes and behaviors (KABs) when testing effectiveness of MedGuides and Communication Plans.

Key findings from surveys of drug developers, health care providers, insurance companies, and others involved in the delivery of health care in the United States show uncertainty regarding the benefits and effectiveness of REMS. Limited evidence is available to date to support existing REMS tools that are working, or to provide suggestions to the pharmaceutical and biotechnology community at large on how to improve the program to meet the goal of mitigating drug risks. Older studies have already shown that printed materials when used alone (eg, MedGuides, DDLs, DHCPLs) are insufficient in changing prescribing behavior and alerting patients to the potential risks involved with a drug, thereby reducing their effectiveness in communicating risks.

In the more than three years since REMS have been required for certain products, very little evidence exists to support which REMS tools are actually reducing the risk of drug toxicity. REMS sponsors should be encouraged to develop more meaningful assessments of how these programs mitigate product risk, or FDA should consider mandating such clinical outcome assessments and post key findings of these REMS assessments for the health care community. All involved in designing REMS would benefit from this valuable knowledge.

4. McEvoy GK. Use of Medication


In the Americas
Conferences
SEPTEMBER 13-14, 2011
The Evolving Clinical Trial Disclosure Landscape
Arlington, VA
SEPTEMBER 14-17, 2011
13th International Paul-Ehrlich-Seminar - Allergen Products for Diagnosis and Therapy: Regulation and Science
Washington, DC
SEPTEMBER 15-16, 2011
Improved Development and Regulation of Transdermal Systems
Arlington, VA
SEPTEMBER 19-20, 2011
Optimizing Dosing for the Safe and Effective Use of Drugs in Patients with Renal Impairment
Washington, DC
SEPTEMBER 20-21, 2011
Improving Clinical Trial Sampling for Future Research: An International Approach
Philadelphia, PA

In the Americas
Training Courses
AUGUST 15, 2011
How to Prepare for a Safety Inspection
Boston, MA
AUGUST 16, 2011
Introduction to Signal Detection and Data Mining
Boston, MA
AUGUST 17-18, 2011
Regulatory Affairs for Biologics
Boston, MA
AUGUST 19, 2011
Overview of Drug Development
Boston, MA
AUGUST 22-24, 2011
Essentials of Project Management
Horsham, PA
AUGUST 23-24, 2011
Introduction to Portfolio Management and Performance Metrics
Horsham, PA
AUGUST 25-26, 2011
Cost and Resource Management in a Multiproject Environment
Horsham, PA
AUGUST 25-26, 2011
Executing and Controlling Projects
Horsham, PA
SEPTEMBER 15-16, 2011
European Regulatory Affairs
Boston, MA
SEPTEMBER 19-20, 2011
Navigating Chemistry, Manufacturing and Controls through the Drug Development Process
Horsham, PA
SEPTEMBER 21-23, 2011
Regulatory Affairs: Part 1: The IND Phase
Horsham, PA

Europe
Conference
SEPTEMBER 26-27, 2011
Joint DIA/EFGCP/EMA Paediatric Forum 2011 - The paediatric regulation in its 5th year: Transition from toddler to school age
London, UK

Europe
Training
SEPTEMBER 19, 2011
Training Course on Advanced GCP Study Monitoring
Paris, FRANCE
SEPTEMBER 19-20, 2011
Training Course on Medical Approach in Diagnosis and Management of ADRs
Paris, FRANCE
SEPTEMBER 22, 2011
Information Day on the New Identification of Medicinal Products (IDMP) International Standards and ICH M5/M2
London, UK
SEPTEMBER 23, 2011
Information Day on the Implementation of Electronic Submission of Medicinal Product Information in the EU
London, UK

China
Conference
SEPTEMBER 21-22, 2011
Supply Chain Management
Suzhou, CHINA

India
Conferences
SEPTEMBER 14-16, 2011
DIA- WHO-EDQM Quality of Active Pharmaceutical Ingredients
Hyderabad, INDIA

Japan
Conferences
SEPTEMBER 5-6, 2011
2nd DIA Cardiac Safety Workshop in Japan
Tokyo, JAPAN
OCTOBER 27-28, 2011
8th DIA Japan Annual Meeting
Tokyo, JAPAN
UPCOMING EVENTS

Regulatory Requirements for the Submission of Investigational New Drug Applications in the USA (INDs)

The Regulatory Development Cycle of a Drug

Online Education

Live Webinars
SEPTEMBER 7, 2011
Bridging the Gap Between Images and Data Management for Clinical Trials

Online Training
SEPTEMBER 8, 2011 AND SEPTEMBER 23, 2011
High Performance Biopharm Teams Online Training Series
Introduction to Clinical Data Management Online Training Series
SEPTEMBER 15, 2011
Electronic Submission Basics: 3-part Webinar Series: Part 1 - eSubs 101: The Transition from Paper
SEPTEMBER 20, 2011
Trial Master File Series Part 1: The Trial Master File—What’s In It and How Is It Managed?
SEPTEMBER 22, 2011
Electronic Submission Basics: 3-part Webinar Series: Part 2 - eCTD 101: Concepts of the eCTD Standard
SEPTEMBER 27, 2011
Trial Master File Webinar Series Part 2: TMF Process Quality Improvements—A Sponsor Case Study and the DIA TMF Reference Model
SEPTEMBER 29, 2011
Electronic Submission Basics - 3-part Webinar Series: Part 3 - RPS 101: Introduction to the RPS (Regulated Product Submission) Standard

EudraVigilance
AUGUST 31-SEPTEMBER 1, 2011
EudraVigilance - Medicinal Product Dictionary (EVMPD) training course
London, UK
SEPTEMBER 5-7, 2011
EudraVigilance Electronic Reporting of ICSRs in the EEA
Zagreb, CROATIA (Hrvatska)
SEPTEMBER 8-9, 2011
EudraVigilance - Medicinal Product Dictionary (EVMPD) training course
Zagreb, CROATIA (Hrvatska)
SEPTEMBER 13, 2011
Introduction to Pharmacovigilance and Electronic Transmission of Individual Case Safety Reports (ICSR) for the use of Eudravigilance
London, UK

Electronic Reporting of ICSRs in the EEA
SEPTEMBER 14-16, 2011 – London, UK
SEPTEMBER 19-21, 2011 – London, UK

Medicinal Product Dictionary (EVMPD) training course
SEPTEMBER 22-23, 2011 – London, UK
SEPTEMBER 28-29, 2011 – London, UK

NEW! DIA has partnered with Thomas Reuters to provide the following IDRAC elearning modules

Access to Unapproved Drugs through Compassionate Use
Basics of Clinical Trials
Basics of Pharmacovigilance
How to Maintain Marketing Approvals in Europe for Centrally Authorized Products
How to Register a New Drug in the USA
How to Register Medicinal Products through the Centralized Procedure
How to Register Medicinal Products through the Decentralized Procedure
How to Register Medicinal Products through the Mutual Recognition Procedure
Introduction to Japanese Institutions and Regulatory Authorities
Introduction to the European Union Institutions and Regulatory Authority
Introduction to the International Conference on Harmonization (ICH)
Introduction to US Institutions and Regulatory Authority (FDA)
Meeting Opportunities with Regulatory Agencies
Orphan Drugs in the USA, European Union and Japan
Overview of the CTD and the eCTD Regulatory Requirements for the Conduct of Clinical Trials in Europe

Regulatory Requirements for the Submission of Investigational New Drug Applications in the USA (INDs)

The Regulatory Development Cycle of a Drug

Online Education

Live Webinars
SEPTEMBER 7, 2011
Bridging the Gap Between Images and Data Management for Clinical Trials

Online Training
SEPTEMBER 8, 2011 AND SEPTEMBER 23, 2011
High Performance Biopharm Teams Online Training Series
Introduction to Clinical Data Management Online Training Series
SEPTEMBER 15, 2011
Electronic Submission Basics: 3-part Webinar Series: Part 1 - eSubs 101: The Transition from Paper
SEPTEMBER 20, 2011
Trial Master File Series Part 1: The Trial Master File—What’s In It and How Is It Managed?
SEPTEMBER 22, 2011
Electronic Submission Basics: 3-part Webinar Series: Part 2 - eCTD 101: Concepts of the eCTD Standard
SEPTEMBER 27, 2011
Trial Master File Webinar Series Part 2: TMF Process Quality Improvements—A Sponsor Case Study and the DIA TMF Reference Model
SEPTEMBER 29, 2011
Electronic Submission Basics - 3-part Webinar Series: Part 3 - RPS 101: Introduction to the RPS (Regulated Product Submission) Standard
What advice would you give to people who are considering a regulatory career?

It’s a very stimulating field, in the sense that routine doesn’t exist in this area: You are always learning new things, and you always have to study new aspects of an issue, so you must be engaged with an issue and ready to study and work hard. You must also be flexible because you have to accommodate others. Especially in pharmacovigilance – you might come to work planning to do one thing, and then suddenly something new emerges. You have to be flexible enough to turn your attention to new issues. You need to accommodate and be responsive to others’ needs.

What is your undergraduate and graduate training?

I am a physician and received my undergraduate and graduate training in medicine in Madrid. When I studied pharmacology in the third year of studies for my degree in medicine, I realized that I very much liked this area of study and wanted to dedicate my professional life to it. I stuck to this idea and when I finished my career in medicine, I started working in this field.

What was the first position that you held in the regulatory field after your medical studies?

I started in the regulatory field in 1991, when I applied for a position with the Ministry of Health in Spain with respect to pharmacovigilance. In 1999, the Spanish Agency of Medicines & Health Products (AEMPS) was created; I joined from the beginning, also in the field of pharmacovigilance. Before that, I worked in both basic and clinical pharmacology. I also spent several early years working in Sweden in clinical pharmacology.

What are some of the most amazing or important changes you’ve witnessed in your career?

One major change I have experienced was the introduction of specialized pharmacovigilance training. When I first started, we were really focused on spontaneous reporting; the subsequent introduction of epidemiology for quantification and analyses was a necessary change. This was really important and stimulating for our field.

The second biggest change is the concept of being more proactive in the conduct of pharmacovigilance by trying to identify new risks, along
with so many changes in ways to communicate these risks to other health care professionals. These are only two of the many changes that I've witnessed throughout my career.

**Q&A Have any job experiences been particularly interesting or inspiring?**

From my experience coming from basic research, moving to clinical pharmacology and then to pharmacovigilance, all my knowledge of basic pharmacology has been a help not only in harmonizing safety issues but also in identifying new safety issues. For example, when I was a Fellow at the Karolinska Institute, I worked a lot on clinical psychopharmacology, and we conducted some experiments in patients with depression. We were trying to identify biochemical markers for depression and responses to antidepressant treatment with platelets as a model for serotoninergic neurons. We measured the serotonin content in patients treated with selective serotonin uptake inhibitors and showed that the serotonin content was really down in patients who were treated with these types of drugs. Then, when I was working in pharmacovigilance, and based on these results, somehow the hypothesis came to us that selective serotonin uptake blockers could lead to an increased risk of hemorrhage, which led some of my colleagues to conduct epidemiology studies in this field. These studies suggested that these drugs could be linked to higher rates of hemorrhage, and these results were replicated by others. This was very stimulating because it linked the whole field of pharmacology together, starting with the basic research, through clinical pharmacology, and then to pharmacovigilance.

**Q&A What role did you play in the EU pharmacovigilance legislation that was passed in December 2010, while Spain served in the EU Presidency?**

The new European legislation on pharmacovigilance was under discussion when Spain, as a Member State, began its six-month term as President of the European Union. This provided a really interesting opportunity to see in the first person the complex process of how legislation is developed in the European Union. It was a very interesting period for me and for the members of my team who also were heavily involved, because we had the opportunity to not only impart new knowledge but to learn how the legislative process works from the inside. We worked with the Secretariat of the Council of the European Union, with Member States of the European Union, with the European Commission and with members from the European Parliament. Very intense discussions about the legislation were held during these months, which yielded a broad consensus in the legislative text.

This was very stimulating because the changes made during the process try to integrate the expectations of the citizens, the Member States and the European Commission. To sufficiently meet the legislative plans and the expectations of all the parts involved was really a challenge. It was quite a nice experience, and we found all the colleagues ready to listen and to make the most of the legislation. It was really a collaborative work, and we were able to end up with something that will be valuable for regulators, the agencies, and for industry, as well as for the patients. We hope that we have contributed to improve pharmacovigilance in Europe, and to have this opportunity was really a privilege.

**Q&A Why have you found time in your professional life to contribute to DIA?**

We all have to share our experience as much as we can through these types of organizations. I really think that DIA offers an excellent forum not only for being up to date with the most recent developments in your own area, but also for exchanging views and communicating with colleagues who work in other areas of the pharmaceutical industry and the scientific environment. It is always very much appreciated and very constructive.
How do you balance your professional life with your personal life?

It is sometimes difficult. I confess that working many hours and traveling sometimes requires the support and understanding of my husband and my sons, who have been very supportive and a great help to me. I have tried to keep some time for them. Your personal life is very important for your growth as a person. Plus, changing your perspective now and then can bring more energy to your work. I try to work very hard to make time for both sides of my life.

Is mentoring or teaching others important to you?

We try to deliver teaching to others working in pharmacovigilance or in related regulatory fields. We also try to engage companies in our country and to collaborate with similar societies and associations. We don’t have as many opportunities as we would like for teaching, but I think that mentoring and teaching are very important. When you have been working in the same field for years, you realize the importance of teaching others from your own experience. It’s how we provide for the future – by teaching and collaborating and creating a good working environment.

How do you explain your profession to people?

When you mention the word “pharmacovigilance,” many people respond, “What is this?” But pharmacovigilance is a public health activity, so I try to explain that after a medicine is approved for the market, there remains a need to follow up on how it “behaves” in the real-world population, or with other drugs that people may be taking.

That’s mainly my activity: To gather and organize and analyze these data so that the drugs we create continue to provide great benefit but with less harm, to help us try to minimize disease. That’s how I try to explain my work.

If you had things to do all over again, would you pursue the same career path?

I don’t know if this is an easy question or not! I am very satisfied with what I am doing, and I enjoy my work very, very much. But there are so many other things in life that I would also like to do! I don’t know: If I had a second life, I probably would like the opportunity for different experiences, perhaps more into nature or more into the humanities, more into the human experience, just to try to experience something else. But I am quite fortunate because I am very happy in the profession that I have chosen.

Is your current data strategy old school?

Turn to Explorys.

Explorys is the fastest growing aggregated healthcare data network for measuring correlations, trends, and outcomes across billions of clinical events.

To learn more, please go to http://explorys.com/dij2011
The DIA 2011 Annual Meeting opening plenary session started with salutations from Illinois Governor Pat Quinn. “It’s a very special opportunity for the people of Illinois and the people of Chicago to greet the entire world,” he said. “We want to thank you for choosing Illinois to come together.” After Governor Quinn’s welcome, Chicago native bluesman Lurrie Bell played the familiar strains of “Sweet Home Chicago” to further set the plenary stage. Paul Pomerantz, DIA Worldwide Executive Director, then delivered his opening remarks.

“Good morning and welcome to all 8,000 of you, who have traveled from all parts of the world, representing 80 countries, to participate in this 47th Annual Meeting. We couldn’t be more pleased to have you here.”

“DIA’s respected position in the world is a tribute to our visionary founders. Sadly, a few days ago, we lost Mr. Thomas Teal, one of DIA’s founding members and our very first Executive Director. Mr. Teal spearheaded DIA’s dramatic growth and development as a global, multidisciplinary, professional association. He will truly be missed. To honor his legacy, DIA is dedicating this meeting in his honor,” Paul explained.

“The meeting theme, Convergence of Science, Medicine, and Health, reflects the convergence of medicinal products with health care policy and delivery, as well as the convergence of technologies, pharmaceuticals, medical devices, biotech, and health information,” Paul continued. “But it also reflects the convergence of DIA’s stakeholders with health care providers and patients to focus on our goal of improved health.”

“Convergence is also reflected in two new features of this meeting,” he said, highlighting the DIA 2011 Patient Fellowship Program and DIA’s first Interoperability Showcase of standards-based information technology solutions.

DIA President Ric Day shared his thoughts about what makes DIA unique. “DIA in the year 2011 truly reflects what DIA has evolved into in its almost 50 years of existence – a global community,” he began. “We’re here in Chicago to work toward a common goal: To contribute to better health outcomes for patients. To realize this goal, we need to listen intently to those who hope to benefit from the fruits of our labors. What is wanted by patients – but actually all of us – is more successful translation of biomedical discoveries into effective and safer medicinal products that accommodate unmet needs, are affordable, and reach patients faster wherever they are in the world.”

After introducing the 2011-2012 DIA Board of Directors, and thanking those Directors whose Board terms have expired, Ric (DIA’s first President from outside the US) introduced incoming DIA President Dr. Yves Juillet (DIA’s first President from Europe) to share his vision of DIA.
“It is quite impressive to address you, thousands of participants expecting so much from this meeting and from DIA,” Yves said.

“We are all aware of the global issues that we have to face in our daily life. DIA is well positioned to help you overcome these challenges – our challenges – with offices and activities in different parts of the world,” said Yves. “But in addition, DIA has to match your needs, which are sometimes very specific and sometimes local – a real challenge. What Paul Pomerantz said in his opening remarks cannot be truer: DIA is about you.”

During this plenary, Dr. David Cocchetto, a former DIA Board President, Drug Information Journal editorial board member, and colleague of Mr. Teal, was given the opportunity to reflect upon Mr. Teal’s foundational contributions to DIA.

“I have the distinct privilege of sharing some brief reflections on Mr. Tom Teal. It has been said that each generation stands on the shoulders of its predecessors; in DIA’s case, the association stands on Mr. Teal’s shoulders,” David began.

“Many of you are aware of his decades of leadership of DIA, as our first Executive Director as well as the founder and first Editor-in-Chief of the Drug Information Journal. Mr. Teal was a leader, trusted advisor, and friend to me and many others. Over 25 years ago, Mr. Teal’s optimism and vision of the grand possibilities for DIA inspired me and others to learn more and do more than we thought we were capable of. When I would meet with Mr. Teal, I could sense just how extraordinary he was.”

“Mr. Teal led by example. He had high expectations of himself, each of us, and this fine organization. By example, he taught about hard work, humility, and embracing challenges. He had a gift for building and sustaining productive networks of people, long before the era of LinkedIn and Facebook. In the 1940s and 50s, he was an Admiral in the United States Navy and a member of the group recognized as ‘The Greatest Generation.’ I knew Mr. Teal as a gentleman and well respected colleague: A man who loved his family, and a man who had a keen understanding of honor, people, and love of country,” he said.

“My thanks and God bless you to the family of Mr. Teal for sharing him with all of us. My thanks to the Board of Directors for establishing and sustaining the Thomas W. Teal Award for Excellence in Statistics Publishing. Thank you,” concluded David.

After introducing and congratulating this year’s Drug Information Journal and Volunteer Service Award winners, Ric presented the inaugural DIA President’s Award for Outstanding Achievement in World Health to the CAPRISA 004 Leadership Team for the AIDS Program of Research in South Africa, which was graciously accepted by Dr. Salim S. Abdool Karim on behalf of the CAPRISA 004 Trial leadership team.

Following a short video, Annual Meeting Program Chair Ken Getz addressed the audience. “The video just shown does something rarely seen today,” Ken explained. “Whether you’re a study volunteer or a professional in the clinical research enterprise, it is rare today to hear public recognition of the incredible and profound contributions that each of you bring to advance public health and medical knowledge.”

“Recognition and acknowledgement of the unique and diverse contributions needed to drive successful drug and device development lie at the very heart of this year’s Annual Meeting theme: Convergence.”

Next, Ken introduced Keynote Speaker Dr. David Ho, Founding Scientific Director and Chief Executive Officer of the Aaron Diamond AIDS Research Center and Irene Diamond Professor at Rockefeller University, and one of the pioneers of AIDS/HIV research. Dr. Ho reviewed the history of AIDS and the resultant quest for safe and effective therapy. Thirty years ago, no one could have predicted the emerging epidemic that currently infects around 2.5 million people each year. “This is arguably the worst plague in human history,” he suggested.

After the ceremonial cutting of the opening ribbon to officially open DIA 2011, plenary attendees left the Ballroom to Lurrie Bell singing and playing “Let’s Talk About Love” – and a world of better health care for all. ■
Once again this year, the DIA Annual Meeting showcased student talent from around the globe with the Student Poster Session, which was held on Monday, June 20, in the Exhibit Hall at McCormick Place. Sixteen well-developed abstracts and posters were presented by students from the US, UK, Macau, and India on subjects ranging from pharmaceutical R&D, risk-benefit assessment, and clinical trials, to MS and depression. The students whose posters were chosen as the top three were honored during an awards ceremony held Monday evening, where they received a plaque and congratulations from DIA President, Ric Day. He encouraged the students to remain involved with DIA as they progressed through their careers, citing it as a great resource for information.

The distinguished panel of judges included:

Barbara H. Gladson, PhD, MS, Director at Biopharma Educational Initiative and professor at the University of Medicine and Dentistry of New Jersey

James L. Parmentier, PhD, professor at the University of Medicine and Dentistry of New Jersey

Danny A. Benau, PhD, the Director of Biomedical Writing Programs at the University of the Sciences in Philadelphia

The following students’ works were selected as winners:

First Place: Anne-Sophie Auroux, Eudipharm
“Meta-analysis of the Efficacy and Safety data Supporting Marketing Authorization of Anticancer Drugs for Advanced Cancers”

Second Place: Brian Claggett, Harvard University
“Estimating Subject-specific Treatment Differences for Risk-benefit Assessment with Competing Risk Event-time Data”

Third Place: Joseph Mburu, Campbell University
“Evaluation of Barriers to Minority Recruitment and Retention in Clinical Trials: A Qualitative Approach”

All 16 student abstracts were published in the July issue of the Drug information Journal (volume 45, number 4). DIA congratulates all the students who submitted and especially the three winners.
Images from the 47th DIA Annual Meeting
BASEL

ECLECTIC, VIBRANT AND HISTORIC

Basel, Switzerland, is sure to captivate visitors with its rich culture, deep history and incredible natural beauty. Located in the northern part of Switzerland and split in two by the Rhine River, Basel rests at the point where the Swiss Jura Mountains, the French Vosges and the German Black Forest converge. It is the third largest city in its home country with more than 190,000 residents. But when incorporating all people living in the area’s trinational agglomeration, the number swells to nearly one million.

Basel boasts the warmest climate in Northern Switzerland, allowing visitors...
to engage in a variety of outdoor activities. The city’s dominant natural feature, of course, is the famed Rhine, which divides the city but unites the region. The southwestern side of the famed river is known as Grossbasel (Greater Basel) and is home to much of the city’s cultural and commercial venues. On the northeastern bank is Kleinbasel (Little Basel), which houses working-class neighborhoods. All of Basel, no matter which bank, holds immeasurable pride in the city’s fascinating history.

Celts, Romans, Huns ... a devastating earthquake, a rampant plague, vicious sacking ... resilience, vision, progress ... these are all important players, events and qualities that mark the grand history of Basel.

The city’s original settlers were Celts, who occupied the area now known as the Cathedral Hill in approximately 500 BC. Nearly five centuries later, Romans established a fort approximately 12 miles east on the Rhine in Augusta Raurica. The fall of the Roman Empire included Augusta Raurica’s demise at the hands of the Alemanns, who moved into the area after 450 AD. Basel was growing—in size and importance—and, in 740, it was named a diocesan city.

Basel experienced major setbacks. In 917, the Huns sacked the city and in 1349, plague claimed nearly 14,000 residents, about half of Basel’s population.

RHINE CRUISES

For a different perspective of Basel, take a cruise on the famed Rhine. The Basler Personenschifffahrt company offers city and harbor cruises that take about two hours and give spectacular views of the Old Town, the Cathedral and more. Basler Personenschifffahrt also offers longer cruises, including brunch and dinner jaunts, and cruises to Rheinfelden. On trips to the latter destination, the boat will be piloted through two locks on its way to the scenic medieval town. The Basler Personenschifffahrt cruises run from May to mid-October and depart from Schifflande. The company’s website is www.baslerpersonenschifffahrt.ch/site/. Office: Rhine at Basel-Gesellschaft AG, Westquaistrasse 62, 4019 Basel; Tel +41 61 639 95 00; info@bpg.ch. Ticket sales and reservations are at Pier 4019, Basel.
located in Grossbasel and provides services to and from Switzerland, France and Germany. Its counterpart, the Basisher Bahnhof station in Kleinbasel, connects with Germany.

Once in Basel, you will find that getting around is easy. Each hotel guest visiting Basel is given a complimentary Basel Mobility Ticket upon check-in. This ticket provides free use of public transport in the city of Basel and the surrounding area for up to 30 days. The public transportation system has nearly 400 stops, even ones in the border towns around Germany and France. You can find all the regional transportation timetables for Basel at www.bvb-basel.ch/en/news/current-info.

Trams are ever present and run every eight minutes during daytime and every 15 minutes in the late evening. You’ll notice that the stops are marked by white and green signs. You can also take the opportunity to go back in history and take a ferry across the Rhine, for a specific purpose or pleasure. The ferries are attached to wires that reach across the Rhine and are powered by the river’s natural current, just as they were more than a century and a half ago.

Signpost tours are a great way to get a 360-degree experience of the
many facets of Basel. For example, in the Altstadt (Old Town), there are a handful of signpost tours—each named after a famous resident of Basel—that begin at Marktplatz. You’ll soon find yourself at the intersection of history and progress as you travel in alleyways that date back to the Middle Ages, take in amazing historic and contemporary architecture and lose yourself in spectacular views.

There are also organized walking tours of Basel that originate from the Stadt Casino’s tourism information office. To help you navigate the city, pick up a city map at Basel SBB Railway Station, the Badischer Bahnhof station, Marktplatz, Messeplatz, Münsterplatz, Aeschenplatz, Schifflände, or Zoo Basel.

**Basel’s Top Attractions**

In addition to its world-class shopping and restaurants, there is much to do in Basel to sate every seeker of culture, history and entertainment. To help you familiarize yourself with the city before you arrive, check out Basel’s official online map at www.basel.com/en/page.cfm/Stadtplan; it features customizable points of interest. For information about guided tours, contact Basel Tourismus, Aeschenvorstadt 36, 4010 Basel; +41 (0)61 268 68 68; info@basel.com.

Here is a sampling of Basel’s top attractions along with their locations and, if available, contact information:

- Basel’s famed **Munster** (Cathedral) wasn’t just built; it evolved. As such, its walls and grounds tell a majestic story of its—and Basel’s—history. Built on the site of the city’s early settlements, the Cathedral, as a structure, began as a 9th century church and, in 1019, was consecrated as a cathedral. It underwent much work over the years, and following the earthquake of 1356 that nearly claimed the entire building, it was rebuilt in the Gothic fashion, which permeated the period’s architecture. Of particular note in the Cathedral are the tombs of Erasmus and Queen Anna of Habsburg, and the spectacularly carved Gallus Forte (St. Gall’s Door), which dates back to the original structure. Münsterplatz, Altstadt (Old Town). www.baslermuenster.ch

- **Basel’s Rathaus in the Marktplatz**

For an incredible view of the Old Town and the landscape beyond, visit the **Basler Pfalz**, a terrace located behind the Cathedral that rises high above the Rhine. A narrow gate will offer you passage from the terrace to Basel Cathedral’s cloister, where you will find the gravestones of members of well-known Basel families dating from the 16th to the 19th century.

Produce and politics are evident at the **Marktplatz**, an open market that is the heart of Basel and is open for business weekdays and Saturdays. Browse among the fresh food and

**FASNACHT**

Basel is home to Switzerland’s most popular festival. The Fasnacht (Carnival)—which dates back to the Middle Ages—is held the Monday to Thursday following Ash Wednesday and features approximately 20,000 participants. It kicks off at 4 AM sharp as masked and costumed musicians play carnival tunes in a procession that moves past throngs of onlookers and through the Old Town. Basel’s lights are dimmed and the city is illuminated most notably by lanterns of the Cliquen (carnival cliques). The revelry lasts for exactly 72 hours, concluding at 4 AM on Thursday.

**TIPPING**

Swiss law requires that all restaurant bills include a service charge that takes the place of a traditional tip. While this negates the necessity of a tip, many visitors do include 10% for good service in restaurants or hotels, or when using a taxi service.
foot high, eight-ton sculpture that constantly swings his hammer up and down in cadence with a human breathing pattern. Built in 1989, Hammering Man is one of a series of hammering men created by Jonathan Borofsky; others can be found in Dallas, Seoul, Los Angeles and Seattle.

The Spalentor (Spalen Gate) is one of three medieval city gates that remain today. It is adorned with the Madonna and two prophets. St. Alban-Tor (St. Alban’s Gate) is an original city gate with parts dating back to the 1200s. Meanwhile, St. Johanns-Tor (St. John Gate) was a portal on the ring fort surrounding Basel that was built following the earthquake in 1356. Spalenvorstadt, Altstadt. St. Alban-Berg, St. Alban.

Spalentor

To get a sense of the depth of the history of the Basel region, visit Augusta Raurica in Augst, just twelve miles from Basel. Augusta Raurica was a Roman town of 20,000 people before being destroyed by Alemannic invaders nearly two millennia ago. The site features a Roman farm and house, and has excavation sites and artifacts on display. www.augustaraurica.ch

For a “wild” time, visit the city’s zoo. Founded in 1874, Zoo Basel was the first zoological garden in Switzerland. It is home to more than 6,000 indigenous and exotic animals that traverse the park-like grounds, indoor/outdoor enclosures, and themed houses. Featured animals include gorillas, rhinoceroses and hippopotamuses. Binningerstrasse 40, Zoo. 061/2953535. www.zoobasel.ch

Opened in 1226, the Mittlere Rheinbrücke (Middle Rhine Bridge) was the first bridge across the Rhine and is therefore Basel’s most historic span. It was commissioned by Prince-Bishop Heinrich von Thun, who, in turn, founded the town of Kleinbasel to serve, in part, as protection for the bridge. In the early 20th century, the wooden bridge was replaced with a stone one to accommodate the new electric trams. Schifflande, Altstadt.

An acknowledgment of the importance of all humankind working together, Jonathan Borofsky’s Hammering Man at Aeschenplatz is a gargantuan 44-

Mittlere Rheinbrücke

flowers, and bask in the grandeur that is Basel’s Rathaus (City Hall), which was built in the 14th century and has undergone expansion through much of its existence. Make sure to note the painted architecture of the building’s exterior painted by artist Hans Bock in the 17th century before going in to see the council chambers, inner courtyard, and tower. Marktplatz, Altstadt.

ECLECTIC SHOPPING

Shopping abounds throughout Basel. For specialty shops filled with local arts and crafts, head to Basel’s Old Town. The main shopping district—which runs on Freie Strasse, Gerbergasse and Spalenberg—offers unique boutiques, and Barfusserplatz and the Bahnhofsareal also offer a wide variety of shops. Typical business hours for shops in Basel are Monday, Tuesday, Wednesday and Friday: 8:30 AM to 6:30 PM; Thursday: 8:30 AM to 8 PM; Saturday: 7 AM to 5 PM; Sunday: closed.
late 1800s, the gallery is run by the city’s community of artists and has gained worldwide acclaim for its dedication to modern art. In addition to its exhibitions and displays, the Kunsthalle has a theater for screening foreign films and viewing video presentations. Steinenberg 7, Altstadt. 061/2069900. www.kunsthallebasel.ch

Meanwhile, the Fondation Beyeler (www.fondationbeyeler.ch) is one of the most famous private art collections in the world, boasting works from Cézanne, van Gogh and Warhol, among others. The museum is located in Riehen, a 20-minute tram ride on the number six service from Basel, and features its astonishing permanent collection and special exhibitions. Baselstr. 101, Riehen. 061/6459700. www.beyeler.com

Artist Jean Tinguely's influence is felt throughout Basel. Fasnachtbrunnen (Carnival Fountain), a shallow pool that features nine whimsical mechanized metal structures that move and spray water, is a testament to the eclectic offerings of the city. It will be sure to earn your attention. Theaterplatz, Altstadt.

For a deeper dive into Tinguely's life and work, roll up your sleeves and visit the Museum Tinguely. The permanent exhibition displays the museum namesake's motor-driven reliefs, scrap metal creations, and sculptures, among others, as you can trace his evolution as an artistic creator and visionary. Paul Sacher-Anlager 1, Kleinbasel. 061/6819320. www.tinguely.ch

In the Kunstmuseum Basel, or Basel Art Museum, you will find the oldest public art collection in the world, courtesy of the Holbein family. The works range from the Renaissance to contemporary and feature the art of, among others, Cranach the Elder, Grünewald, Böcklin, van Gogh, Gauguin, Cézanne, Picasso and Braque. St. Alban-Graben 16, Altstadt. 061/2066262. www.kunstmuseumbasel.ch

For a museum with a decidedly contemporary focus, plan to spend some time in the Kunsthalle (Basel Art Gallery). Established in the

BASEL FAST FACTS
- Population (Basel): 190,000
- Population (tri-national agglomeration): About 1 million
- Language: German
- Currency: Swiss Franc (CHF)
- Climate: Relatively mild, with summer highs reaching near 80°F and winter daytime averages around 35°F
- Country dialing code: +41
- Telephone area code: 061
- Emergency: Dial 117 for police, 144 for ambulance, 118 for fire
- World time zone: UTC / GMT +1
- Best Buys: Basel offers a wide array of shops to purchase jewelry, watches, antiques, art, chocolate, local crafts and much more.

Useful Websites:

Plan to attend
DIA’s 5th Annual Clinical Forum, Cross-Functional Working for Better Results
Basel, Switzerland, 10-12 October, 2011

VOL 3 ISSUE 4  GLOBAL FORUM
Following DIA Path from Student to Professional

Dan Daneasa currently works as Regulatory Affairs Coordinator for Merck Sharp & Dohme (Europe) Inc. in Brussels, Belgium. After completing his pharmacy studies, Dan began to attend DIA events in Europe, found his niche in our association’s multidisciplinary, international member network, and through this network found his first professional job. In the following article, Dan shares highlights of his journey from student to professional for our Global Forum readers.

In September 2009, I graduated with a degree in Pharmacy from the University of Medicine and Pharmacy in Tîrgu Mureș, Romania. Throughout my years of study, I was actively involved in the European Pharmaceutical Students’ Association (EPSA), and in April 2009 was elected for a one-year mandate as Vice President of Mobility. This was unpaid volunteer work, and communication was mainly done by email and regular teleconferences – much like, I would later discover, the Special Interest Area Communities (SIACs) offered by DIA to our members.

After graduation, I worked for a few months in my family’s community pharmacy. I soon realized that while working in a community pharmacy is rewarding, I wanted a bigger challenge: I wanted to work in the pharmaceutical industry. During this time, I began to attend educational events in Europe, and took advantage of every opportunity to network with pharmaceutical industry professionals.

My first DIA experience was attending the 3rd Annual Clinical Forum in Nice in October 2009, as one of 200 EPSA students invited to attend the Forum symposium. Later that year, I began to apply for job openings and participating in job interviews. One of my very first interviews was for a traineeship in Regulatory Affairs offered by a generics company in Hungary. When I returned home from this interview, I got my first professional opportunity: I received a telephone call from the European Medicines Agency in response to a traineeship application I had submitted online a few months before, and had almost forgotten about. During this telephone interview, I clearly showed my willingness to learn and shared all I knew about pharmacovigilance. I was offered a trainee position in the pharmacovigilance sector.

I was eventually offered the job in Budapest as well. But after much careful thought, I made my choice: My destination was going to be London, not Budapest, and I was going to start at the European Medicines Agency (EMA) on 1 January, 2010. During my traineeship at the EMA, I was able to continue my mandate in EPSA, and worked late hours both at the office and at home to prepare the upcoming annual EPSA student Congress. With my ESPA function, I was able to obtain an interview with Mr. John Dalli, the EU Commissioner for Health at DG SANCO, regarding his European health policy objectives, which was published in EPSA’s newsletter. It was like having two different jobs at the same time: One involving high-level policy and another one involving the practical technical details of pharmacovigilance. I enjoyed this diversity very much.
My second big professional opportunity arrived when I attended the DIA EuroMeeting in March 2010 in Monaco via the DIA Student Fellowship. I collected almost 100 business cards, going from stand to stand in the exhibit hall, networking and meeting people. I also attended many different sessions to learn about pharmaceutical hot topics – I was convinced this knowledge would give me an advantage during my future job interviews. At this meeting, I met with DIA Advisory Council Europe (ACE) members for the first time. Along with several of my EPSA colleagues, we discussed possible collaborations between our student association and individual pharmaceutical companies.

In April 2010, my mandate with EPSA ended. I recall thinking how much I had accomplished during one short year of volunteering, and how my life had surely been changed for the better. This was also when I realized the usefulness that professional associations, made up of motivated people, can have for their individual members. I decided that I wanted to get more involved with DIA. That June, as my traineeship at the EMA was coming to an end, I realized that if I wanted to see my dream of joining DIA come true, I would need to find a job in the industry. But, how to find a job?

One look at the DIA website provided me the answer: I discovered the Regulatory Affairs Forum which DIA presented just five minutes from the EMA office in Canary Wharf, London. I attended this event, where I again met people I knew from Monaco and was introduced to the Executive Director of Regulatory Affairs Europe of MSD, who was also attending.

I had just met my future boss.

All the information I had learned through my DIA experiences was very helpful during interviews I had with senior MSD staff in Brussels. As a result, I was offered the job of Regulatory Affairs Coordinator for MSD and started working in September 2010. My professional development continues and I am now building my experience in Regulatory Affairs by learning about European regulatory legislation, procedures, and processes. After approximately one year of working in Regulatory Affairs, I am still smiling! I enjoy my work, no day is like the other, and I am very motivated to continue on this path.

Shortly before leaving Romania for Belgium, I also enrolled in a distance-learning Masters program in Biostatistics at the University of Bucharest. I got the idea to study statistics during my traineeship at the EMA, when I saw the importance of biostatistics. This impression was also confirmed by presentations I attended at DIA events.

My New Year’s objective for 2011 was to apply for the DIA Emerging Professional Fellowship and to attend the DIA EuroMeeting for the second time. My amazing experience at the DIA 2011 EuroMeeting in Geneva convinced me to become a DIA member in April 2011, and I am now a member of the DIA Professional Education, Training & Development SIAC.

It is a great honor for me to be able to share these DIA experiences with the readers of our Global Forum.
The 3rd DIA China Annual Meeting was held in Beijing on May 15-18, 2011. During that meeting an important forum on “Scoring the Chinese New Drug R&D Ability” took place. Moderated by Ling Su, DIA President-Elect, the participants included Yi Feng, Ning Li, Wei Zhang, Xianping Lu, Zhe Yang, and Ruiping Dong.

These distinguished panelists offered responses to questions posed by Ling Su, including the current level of innovation and novel drug development in China, from both industry and government policy perspectives; the recent policy of the “Thousand Talents Program,” which encourages Chinese talent working internationally to be returning “sea turtles” and return to their homeland to conduct R&D, participate in formulating policy with the government, and influence decision making as it applies to new drug R&D and regulatory affairs.

Ling Su then posed this to the panel: “The flower of innovation” is in bloom in our ancient country. China is progressing…to a strong drug innovative country. Please give a score for the current innovative drug situation in China, if ten is the highest score.”

“If we are looking at each part of the Chinese pharmaceutical industry, many key parts have competitive advantages.”

Ning Li

“The current situation in China is the best ever for R&D of novel drugs.”

Zhe Yang
The panelists offered their scores and comments on this request, and Ling Su summarized the results as follows:

**Conclusion**

Ling Su: Before telling you the mean score, please allow me to summarize this historically significant forum. There is no doubt that China has some advantages in earlier stages of new drug R&D; however, the ability for late stage development should be improved. There are a large number of junior talents; however, we are lacking talents with skills in decision making and strategic planning, as well as top-level talents who are able to interact with government at a scientific level. From the esthetic point of view, there is no perfect thing in the world, so a score of 10 may be a false proposition. Therefore, if we suppose that 9 is the highest score, then the mean score for today’s new drug innovation in China is 4.5. In other words, China’s journey to become a strong innovation country has gone half way over several decades. However, we still have half way or even longer to go. Let’s look forward to the day of harmony and win – together!

---

In the future, we will put more effort into constructing the technical guidance system, and use these guidelines to guide our R&D and review activities.”

**Wei Zhang**

“Many international companies have closed their R&D centers in Europe and the US and set up new centers in China due to the financial crisis.”

**Ruiping Dong**

“China will catch the opportunity if we can see this trend clearly and apply a review and R&D process to meet clinical demands.”

**Yi Feng**

“Ten years ago, many overseas returnees, myself among them, brought innovative ideas when they returned to our country.”

**Xianping Lu**
Selecting a Vendor for a Central Lab

Deepti Sanghavi

In the last few years, central laboratories have gained increasing importance as a response to the need experienced by the growing number of multicenter clinical trials in India. As the breadth and depth of services required from central labs continue to increase, we look at various aspects of selecting the right vendor for critical central lab services.

The sponsor can take these points into consideration while auditing a central lab before the start of the study.

1. Documents
Lab accreditation and certification documents -
- to determine to which international standard the laboratory works eg, ISO/EN/EC, CAP, NABL, GLP, GCP.
- The prospectus of the laboratory and description of the services offered, such as immunochemistry, biochemistry, special immunochemistry, hematology, molecular biology, microbiology, genetics, etc.
- Job description, CV, and training records of lab personnel.
- List of SOPs, guidelines, work instructions, and manuals. SOP for all the tests detailed above, as well as for IT, QA, CR, and nontechnical processes. The organization should also follow standard GLP and GCP practices. These SOPs should be periodically reviewed and approved. All the earlier SOPs should be superseded, and training should be done on new SOPs.
- Organogram-An organizational chart which identifies key personnel, eg, project/study/ account managers, laboratory staff, data manager, IT staff, internal QA staff.
- Audit conducted for any subcontracted parties or courier services.
- Inspection findings by CAP/NABL and resolution of the same. If any inspections have been performed, the auditor should review the reports and, if applicable, any preventive or corrective actions. Verify that the corrective actions have been implemented.
- Quality policy and Quality Manual-The auditor should check that it is current and has been authorized by upper management.
- Business continuity plan, disaster management plan.
- Lab normal reference ranges.

2. Facilities
A key task of any laboratory audit is an extensive tour of the facilities. In order to have an overall impression of the facility, the auditor should review the following:
- The procedure available for the activities to be performed at the laboratory, eg, the handling of the results of routine laboratory tests and communicating the results to the sponsor (entire workflow from the receipt of samples from site, the analyses of samples,
and reporting of results to the investigators and sponsor).

- Sufficient storage space in the facility area.

- The receipt, processing, and storage areas with regard to the re-labeling of samples, safety procedures used, temperature control of the premises and, where applicable, equipment, hygiene, and security (e.g., fire protection alarms).

- The overall impression of the laboratory, e.g., cleanliness, safety provisions for staff, such as use of white coats, gloves, eye protection.

- The procedures in place for the management of laboratory waste and its disposal. Special attention should be paid to the disposal of hazardous waste such as radioactive or infectious materials.

- The archiving facilities of paper and electronic records and retention/destruction procedures for biological specimens.

- The security systems should be evaluated. This should include verifying that access to the facility is controlled.

- Back-up systems: provisions in case of power failure, contingency plans for mechanical failure of systems or shutdown of entire systems, departments, etc.

- Validation of computer systems and compliance with 21 CFR Part 11.

The auditor should obtain information concerning the following:

- The capacity and type of clinical sample analyses performed per day and per year.

- The number and type of clinical studies (including the number of sponsors) handled by the laboratory at any one time.

3. Equipment and Reagents

The auditor should ask the staff to explain how critical tasks are executed. For critical steps and/or equipment, written instructions should be compared against actual work practices during performance of an analysis/task. The following should be covered:

- A list of equipment that details the name, model/type and year of manufacture, the date the equipment was placed in service, the range and accuracy, date of last calibration, calibration due date, and vendor through which calibration was done, for each piece of equipment.

- Back-up equipment and procedures for each machine in case of instrument failure, e.g., analyzers, incubators, freezers, refrigerators, centrifuges, pipettes of various types.

- Procedures and their implementation for monitoring calibration and standardization of equipment. Documentation of day-to-day performance and functioning documented in log books. The auditor should look for evidence of calibration of pipettes, evidence for daily calibration of analyzers and freezers. Written procedures and documentation, such as logbooks, for service/maintenance of equipment.

- Documentation of the installation of equipment (installation qualifications) and further verifying whether maintenance contracts have been in place during the entire life cycle of a given piece of equipment and whether contractual agreements have been adhered to.

- Materials stored in compliance with laboratory procedures and/or suppliers’ instructions.

- Labels on reagents/materials show source, identity, concentration, expiry, and opening date, lot number, storage conditions.

- Inventory Log for reagents and materials and responsibility for ordering reagents/materials and maintaining the inventory log.

- Temperature monitoring of freezers and refrigerators.

- Alarm systems and documentation of the test of alarms.

- Availability of and compliance with SOPs for handling and documenting “out-of-specification” periods.

4. Kit Preparation and Investigator Support

The central lab needs to be trained by the sponsor on protocol-specific tests, visit schedule charts (to deliver kits to the site), and the specific temperature range for transportation.

The central lab should be able to provide the site with sampling kits, which generally include tubes, labels, pro forma invoices, airway bills, kit requisition forms and boxes for the dispatch of the sample tubes as well as a protocol-specific Investigator Instruction Manual which details the procedure for drawing, handling, processing (centrifuging) and
dispatch of samples as well as contact numbers and a communication plan with courier services. A dummy run dispatch of lab kits should be done before the start of the study. The auditor should review

- Requirements for any special containers or lab kits.
- The type of kit available, quality control (QC) procedure for the kit preparation such as percentage of checked kits, review of kits, eg expiry dates, procedures for review and approval of labels, kit contents, etc.
- The compliance of packaging materials and procedures with IATA regulations.
- The procedures for the recall of faulty materials sent to sites and procedures for handling complaints.

It is important to be clear on the task ownership matrix between the central lab, sponsor, and sites. Also, the communication plan and the risk management plan need to be finalized before the start of the study.

5. Transportation
The auditor should ascertain the following:

- If couriers are used, the procedures of the courier for being contacted by investigators, picking up samples, documenting receipt of samples, storing packages, documenting delivery of packages to the laboratory, and biological safety precautions.
- Contingency arrangements with the courier in case of strikes, customs problems, or transportation problems.
- Temperature monitoring during transport, documentation at the central lab’s end, and communication of the same to the sponsor. Procedures to follow in case the temperature of the sample is out of range.
- Interactions between the laboratory and the courier company, such as monitoring the courier’s performance and procedures to give feedback to the sponsor in case of unsatisfactory performance on the part of the courier. Also, it should be confirmed whether the shipment can be tracked via Internet.

6. Receipt, Handling, and Processing of Samples
Receipt of samples is a critical step, as they may be re-labeled and stored until the analysis is performed. The following should be reviewed:

- The system for registering and, if applicable, labeling the samples and recording the date of sampling, receipt, analyses, and date and time of reporting the results.
- Procedures for the confirmation of receipt of the samples to the investigator and/or the study monitor.
- Feedback to the clinical trial site if the quality of samples and/or documentation is inadequate.
- Procedure to be followed in case of incomplete/wrong/missing information by raising a DCF (data clarification form) to the site.

Obtain and review the flow chart, describing the overall progress of samples in order to identify the critical processes such as:

- The identification of samples throughout the workflow.
- The splitting of samples for analysis, as routine samples and clinical trial samples are handled differently.
- QC procedures for sample processing.
- Calibration and validation of systems.

It is also important to be aware of laboratory opening hours, procedures for the receipt of samples outside working hours, arrangements for coverage because of staff illness, vacation, and public holidays.

7. Storage of Sample Until Analysis
The following should be ascertained by the auditor:-

- Tracking and storing samples until analysis is begun.
- The process for obtaining missing information from clinical trial centers and documentation of this process.
- The procedure for handling unscheduled samples.

8. Sample Analysis and Retention/Destruction
The following should be reviewed:

- Procedures for handling and documenting deviations from standard practice. This includes the assessment of the rationale, risk/impact evaluation and follow-up action by the responsible scientist.
• Systems and procedures to avoid contamination / cross contamination of samples, reagents and test kits.

• The procedures for handling abnormal test results including sample re-analysis and analyses performed outside the protocol time window.

• The handling of “out of specification” results

• The final destruction of back-up samples and the roles and responsibilities of any personnel involved in this process.

• The health and safety provision for the handling of infectious samples (biohazards) and potentially infectious samples (HIV, Hepatitis etc).

9. Reporting to Investigator and Transfer of Data to Sponsor

The auditor should look into the following:

• Procedures should be in place to promptly report the results to the investigator (eg, fax followed by mail) and sponsor, if necessary.

• The central lab should provide an average turnaround time (TAT) of dispatch of lab kits as well as generation of reports from the time of receipt of samples.

• The timelines for faxed reports when laboratory test results are needed, eg, to determine the selection of patients during screening and randomization.

• Procedures for flagging “out of range/alert” results. Procedures for promptly contacting the investigator or the sponsor if clinically significant abnormalities are detected in order to have a medical evaluation and enable the investigator to take appropriate action.

• Validation of electronic transfer. Procedure and system used for the data transfer, eg, real-time release, batch-wise electronic transfer, or diskettes. If data are transferred electronically, verify that the data transfer is encrypted. Data management specifications—transfer of data (eg, electronically, encryption, email, ASCII file, Excel sheet, online in batch mode or real-time). When appropriate, before the study starts live, a test transfer can be sent to the sponsor. Alternatively, integration of EDC with IVRS and central lab systems should be done.

The factors which can be considered while selecting and managing a central lab for success can be summarized in the following points, and a decision should be based on all the points discussed above plus the following:

• Cost.

• Time zone difference in case the central lab is outside the country.

• Transportation time and sample stability.

• Sample kit availability and dispatch time to sites.

• Availability of appropriate shipping license.

• National and international holidays.

• Communication between sponsor, site, lab, and courier services.

• Flight delays.

• Periodic progress reports to the sponsor.

• 24/7 help desk support to the site and sponsor.

Clearly, the project manager at the central lab plays a very important role in steering the study forward to its successful completion. Researchers currently need laboratories that are able to give value-added services, including a wide variety of tests, standard and calibrated lab equipment, delivery of lab kits on time to sites, training site personnel to take blood samples, packaging and sending the shipment, cold chain maintenance, specimen analysis, and providing progress reports to sponsors.

Reference

European Forum for Good Clinical Practice, Guideline for Auditing Clinical Laboratories.

Dr. Deepti Sanghavi is Medical Advisor-Clinical Research, Wockhardt Limited, in Mumbai. Readers can contact her at dsanghavi@wockhardt.com.
5th Annual Conference in Japan for Asian New Drug Development

Hironobu Saito

The Fifth Annual Conference in Japan for Asia New Drug Development was held on 11-12 May at the Tokyo Dome Hotel.

After the earthquake and tsunami in Japan, a number of conferences and workshops were canceled. However, due to the encouragement and strong support from program committee members in Korea, Taiwan, and the Chinese mainland, we were able to hold the meeting. As the program chairperson, I would like to thank everyone who participated and contributed to the timely and important discussions that took place.

The main topics for discussion were oncology, pharmacogenomics, and GCP compliance and inspection in Asian drug development. For the oncology session, several early-stage oncology studies in East Asian countries were introduced, and the Asian contributions to global development were presented. Recently, East Asia has become an important territory for early-stage development in the oncology therapeutic area. During the pharmacogenomics session, Asian activities in PGx-based medicine were highlighted, and practical examples such as the Taiwan Stevens-Johnson Syndrome, Japan: Usefulness in Japanese Population were introduced. In the GCP compliance session, the experiences in the Chinese mainland and within Japanese companies were introduced.

For five years, I have felt confident that Asian collaboration has advanced and that the Asian contribution to global development is an indisputable fact. The final goal of this conference was to make contributions to patient care in Asia. To achieve this, we plan to maintain closer communication among Asian countries. In cooperation with other Asian colleagues, Japanese members hope to make contributions to global public health.

I look forward to seeing you at future conferences.

Hironobu Saito, PhD, served as Program Chair for this conference. He is Director, Global Regulatory Management Group, New Drug Regulatory Affairs Department, R&D Division, Daiichi Sankyo Co. Ltd.
Networking opportunities at DIA 2011 included the annual DIA Japan luncheon on Wednesday July 22. Approximately 200 participants from Japan simultaneously enjoyed lunch and remarks delivered by several members of DIA’s executive leadership team: Ko Sekiguchi, Director, DIA Japan LLC; Paul Pomerantz, Worldwide Executive Director; Dr. Ric Day, DIA Immediate Past President, Board of Directors; and Dr. Yves Juillet, DIA President. A special presentation was also delivered by Dr. Tatsuo Kondo, Chief Executive, Pharmaceuticals & Medical Devices Agency (PMDA), Japan.
The need for harmonization of regulatory standards for clinical trials being conducted in Latin America was highlighted at a series of sessions at DIA’s 47th annual meeting in June which focused on strengthening the regulatory framework in these countries by addressing the disparity in such areas as reviews and inspections, post-market research, drug safety, marketing surveillance and quality control monitoring, to name a few. The speakers included Paul J. Seligman, MD, MPH of the office of International Programs of the US FDA, Eduardo Johnson, MPH of the National Health Institute of Chile and Dr. Martha Parra Diaz, Director of COFEPRIS (Committee and Research, Comision Federal para la Proteccion contra Riesgos Sanitarios).

In his slide presentation, Dr. Johnson stated that Chile is currently working on a bilateral agreement with other Latin American regulatory agencies, including INVIMA in Colombia, ANMAT in Argentina, ANVISA in Brazil and COFEPRIS in Mexico, as a means of achieving “regulatory harmonization that will make way for the easy exchange of medicines with quality standards that will be accepted for the Latino American countries.” While he cites strengths such as “management is highly committed to a quality assurance system” and that “legal bodies support regulatory activities,” he also pointed out weaknesses in the clinical trial process that includes “no formal accreditation training in Good Clinical Practices of the researcher and his team.”

In Mexico, similar challenges exist, according to a power point presentation given by Dr. Martha Parra Diaz who believes that “inspection programs for research sites and the inclusion of new research sites among the social security institutions” would aid greatly in the achievement of clinical practice standardization. She also supports the authorization of “an Ethics Committee in every state in the country and main referral centers.”

Dr. Seligman provided statistics in his presentation on current clinical trials being conducted worldwide. There are “greater than 200,000 patients enrolled at over 6,500 foreign sites” and “Central and South America regions contained 26% of all subjects enrolled at foreign trials sites, but they accounted for only 7% of foreign sites.” He further pointed out that “the average number of subjects per site was more than three times as large for Central and South American countries as for Western European countries.” Efforts to harmonize standards in the region are ongoing and it is important to understand the country-specific regulatory frameworks and approaches when attempting such comprehensive regulations.

8th Latin American Congress of Clinical Research Latin America Role in Worldwide Clinical Research

Panamericano Hotel and Resort, Buenos Aires, Argentina
Oct 19 2011 7:00am - Oct 21 2011 3:00pm

Interest Area(s)
Clinical Safety/Pharmacovigilance,Clinical Research,Project Management,Regulatory Affairs,Research & Development

Overview
This three-day congress will include two pre-congress courses and a two-day conference focusing on both the global and regional aspects of clinical research.

Featured Topics
• Cell-Based Therapies: The New Drug Class
• Latin America Regulatory Affairs Update
• First Time in Man & Early Phase Trials
• The Contribution of Latin America to Data Quality on Marketing Applications
• Clinical Safety and Pharmacovigilance
• Ethical Issues: A Permanent Dilemma
• Endpoints, Surrogates and The Rationale on Study Design
• Streamlining Logistics in the Region
• Sponsoring of Clinical Research by Nontraditional Players
• Biosimilars and the road ahead

Pre-Congress Courses
October 19th
# 1 Risk Project Management
# 2 Clinical Quality Assurance: The Basics

Use Event Code 11902 to register at www.diahome.org
MAKE CHANGE HAPPEN
Create the Future through Leadership

In an increasingly competitive global marketplace where change is hastened at an astronomically rapid rate, those companies that cannot envision change and drive it forward are bound to fall far behind their competitors. Yet, the majority of those organizations which do attempt to implement change are unsuccessful. In fact, research conducted by Ken Blanchard Companies indicates that up to 70% of change efforts fail or get derailed, and those failed efforts can lead to huge monetary losses as well as defeated morale.

So, how can you lead your organization through a successful change initiative? It takes foresight, leadership, communication, cooperation, employee empowerment and a willingness to embed those changes deep within the corporate culture. And, it all starts with a single impetus: a corporate-wide sense of urgency that shatters inertia and creates the momentum to unite employees behind a viable change vision.

Getting the Change Process Started
Today’s businesses need to make changes that will sharpen their competitive edge. Yet, in order to initiate change on a large-scale basis and achieve success in a timely fashion, especially among diverse departments, a sense of urgency is imperative.

If the corporation were a ship, the captain would tell his crew that the boards in the bottom of the vessel were perilously in need of repair. If we don’t tend to them now, we will soon be bailing out just to keep our heads above water: We need to take action now! On your “ship” it may be that the company is losing market share, customers are switching to the competitor, there are heavy third-quarter losses and jobs are on the line.

Initiating change must start with a frank depiction of the current state of affairs within the organization. When employees comprehend the specific problems, and unite with a clear understanding of the need for immediate adjustments, they will be more willing to step up to the plate.

“Most change within a company comes about for continued survival,” affirms Richard Deems, PhD, and co-author of Leading in Tough Times. “People need to understand that; and they need to know the ‘why’ behind the change. Give them the reasons up front and you will develop their support for the change. Without a sense of urgency, most people will dig their heels in and fight you every step of the way.”

After all, it takes hard work, sacrifice and willingness on the part of a large number of employees to accomplish a change vision. It’s no wonder that people need a highly persuasive...
reason to engage in a long-haul effort.

“We get comfortable with what we’re doing,” says Don Mroz, PhD, Dean of Post University’s Business School, “but this is dangerous, particularly in the competitive environment that we’re in right now. Without that compelling sense of necessity for change, an organization can become stagnant. You must find a way to engage your workforce. Involvement is the key. Complacency holds businesses back.”

Mroz suggests you raise the level of dissatisfaction regarding the current state within your organization, multiply that by your vision for the future and multiply it again by some first steps. If all of that is greater than the resistance to change, then your company will start to move in a new direction.

Who Will Lead the Change?
According to John Kotter, respected change leadership guru—and author of Leading Change, A Sense of Urgency and Our Iceberg is Melting—after you establish a pressing need for change, you must then create a guiding coalition who together will build a clear change vision and will develop workable strategies to drive the initiative forward.

“Individuals, often representing a cross section of the organization, will volunteer for a seat on the guiding coalition with the understanding that this responsibility is above and beyond their day job,” explains Kathy Gersch, founding member of Kotter International. “You want a diverse group that offers a wide range of perspectives. If you choose well, you create a sort of octopus with lots of tentacles that reach out across the divisions and can engage people and maximize support for the change effort.” She also affirms that having a volunteer panel brings power and creativity to the process. “You capitalize on the energy associated with a ‘want-to mentality’ and unleash these ambassadors of change within their various circles of influence.”

With the help of a facilitator, the guiding coalition can then process the common goals and create a change vision. The guiding coalition will determine how the organization needs to operate to achieve these goals and will define initiatives that can move the company in a new forward-thinking direction.

Not only is the coalition able to reach people closest to the processes that need to change, but it can also effectively communicate across initiatives. Gersch gives the example of a work-life committee that saw the absence of nearby childcare facilities as a huge deterrent to progress. Coincidentally, the R&D department voiced its need for larger facilities that were not in its budget. When the work-life group got funding to build a daycare center, they included space for R&D. Instead of problems staying in separate silos they become connected across the change effort—a powerful side benefit of a guiding coalition that has breadth of perspective.

Bring the Vision to Life and a Voice to the Vision
“If you are going to succeed in achieving a major change initiative, all of the stakeholders need to be involved, engaged and aligned,” says Sekani Michel Williams, president of Watershed Strategies. “You need to gain their understanding of: what it is you are trying to accomplish, how the company can get there [the strategic plan] and what their individual roles are in making that happen.”

When formulating a vision and strategy, Williams suggests breaking the vision down into categories, drawing the goals out in a map and then creating a theory of how to make the vision come to life. Name specific activities and projects that need to be taken on, write down how these are going to be achieved and assign someone to be accountable for the success of each initiative.

Once the vision and strategy are clearly stated so that they can be understood by all stakeholders, then they must be properly communicated.

“Your goal is to achieve a shared vision,” states Mroz. “Over communicating is what it takes to cement that vision in. Yet, most leaders under communicate the change vision. You need to draw people in so that they feel part of the bigger picture. By offering a clear, concise vision and personalizing it as much as possible [what’s my role in it? what’s in it for me? how can I make a difference?], you get people to rally around it.”

“Over communicating is what it takes to cement that vision in.”

On the other hand, if it is not clearly communicated, the vision becomes loose and incongruous and runs the risk of sounding too autocratic, says Mroz. He feels leaders need to make their change vision meaningful for people and they need to encourage two-way communication so that there can be a real conversation around it. People must be able to internalize the vision and integrate it...
into who they are. It’s also important that it align with the personal values and vision of the workforce. Above all, he says be sure to use multiple forms of communication: conversations, town hall meetings, water cooler chats, departmental meetings and work groups to reinforce the change vision.

“Passion is important,” he adds. “Talk from your head and heart. Emotion shows people you really believe in the vision and it shows you are a real human being who wants to help them and the organization succeed.”

In his book Leading Change, Kotter underscores the fact that the change vision must be communicated in a way that is “clear, simple, direct, uncomplicated, memorable, consistent and often repeated.” Marian Thier, president of the coaching firm Expanding Thought Inc. and Listening Impact, agrees and adds that the change vision message must be crafted so that it reaches out to four distinct listening audiences:

- **Self-concerned Inner-Personal Listeners** who want to know: “How will the change impact me?”
- **Outward-looking Extra-Personal Listeners** who need to understand how the change initiative will affect others: their employees, their department, the organization
- **Problem-Solving Listeners** who want all the facts and details of the change before getting on board in order to weigh its effect on current problems and determine its feasibility
- **Conceptualizing Listeners** who listen for ideas and look to make the vision for change bigger

Repetition is essential when communicating a change vision, Thier adds, and she points toward research that shows in order to effectively communicate a change vision you must reach out to your audience at least eight times, using at least three different modalities.

Furthermore, it’s important to communicate a change vision in person as well as in writing, says Deems. He advises leaders to make the initial announcement in person early in the week, early in the day—and then to stay visible. “Don’t hide away in a locked office; a closed door makes employees nervous and suspicious. Walk the halls, be accessible, keep an ear open for comments and get a sense of how people are reacting to the vision,” he says. “Allow discussion and questions to percolate among those involved in the initiative—and get those questions out in the open.”

Recognize and Empower the Real Change Heroes

Corporate change is about getting as many people as you can on board the change effort, says Tom Armour, co-founder of High Return Selection. “Smart people drive change and drive it well once they sign on,” he says. “When groups of employees are empowered, the success becomes infectious, and exponential.”

To empower employees, Armour suggests that you start by getting them excited about the change and then do everything in your power to provide recognition to those who affect change and are part of the solution. Make them heroes within the organization and do so publicly so that others see that individual efforts are being valued and appreciated.

“When groups of employees are empowered, the success becomes infectious, and exponential.”

Jenny Schade, president of JRS Consulting, identifies another key aspect of empowerment: make sure employees understand that their efforts are part of a larger vision. She points to the tale of the two bricklayers. Working side by side, each is asked the same question: what are you doing? The first mason says he is building a wall; the second responds “I’m building a cathedral.” Whose work do you think will shine? “Companies need to make sure employees know what the vision is, but, as importantly, employees need to understand how they support that vision and how their efforts are having an impact. It’s important to empower employees by letting them know that they are an important part of the big picture,” says Schade.

Equally crucial, she adds, is making sure your employees have the tools (skills and training) that will empower them to do their best.

Marv Russell, author of Linebacker in the Boardroom, says creating an environment for success starts with a leader who can engage a workforce by earning and then developing a strong level of respect and trust. He can lead the way to success through encouragement and by investing...
time in developing the capabilities of
his employees.

Energize Efforts via Short-term Wins
The reason for planning short-term wins is to help sustain enthusiasm for the change effort and demonstrate to employees that their hard work is paying off. “It’s easy to get demoralized when the vision is so grand and seems so far off in the future that the reward is disconnected from your day-to-day activities,” says Williams. “It’s important to give employees a sense that what they are doing is worthwhile, is going to be recognized and is working toward that larger goal.”

When planning the change vision, Williams advises leaders to be sure to include some short-term goals. “Break the long-range goal into smaller more manageable chunks that can be accomplished and rewarded more quickly. In that way, employees are able to see the results of their contributions in quarterly improvements and can envision the gradual buildup that will result in a major change down the line.”

In addition, he suggests letting each team see the results of the other teams. “Scorecards are a great way to show how each division is doing—they make results visible and encourage an open dialogue between departments. Everyone wants to know what the most successful team is doing so that they can incorporate those tactics or approaches into their own change effort.”

“Short-term wins build credibility for the whole initiative,” says Schade. “Get employees directly involved in the process. Let them identify what success looks like and determine when they have been successful. Then, internally convey these wins to the rest of the employees. In this way, it feels less like a management initiative and more like an employee initiative.”

Look at Gains, Yet Champion Change
Gersch warns not to let short-term wins result in a loss of focus or a buildup of complacency. “This is often the point at which many change efforts fail to reach their long-term objective. As progress becomes evident, there’s a tendency to let up on the pedal and slip back into the old way of doing things,” she says.

It’s a critical stage and she often advises companies to bring new people, new skills and new initiatives on board at this time because there is still a lot to be accomplished before the ultimate opportunity is reached. It may be time to put a new guiding coalition in place to refresh the energy and to evaluate how far the change effort has come and to gauge how far it still has to go; this will keep things moving forward.

Make Successful Change Stick
After successfully implementing change, an all-too-common mistake is failing to anchor the new approaches into the corporate culture. Armour says he has seen many companies slip backwards due to a failure to ingrain the new approaches, processes or tools. “Human beings will often revert back to their old and comfortable ways if those ways are still accessible,” says Armour. “To anchor new approaches, the old ways need to be dismantled, but this is easier said than done. Those old ways may be supported throughout the company’s culture in business planning, management practices, performance and reward systems, hiring methodology, and more,” he points out.

To avoid seeing change break down, Armour asserts that leaders and managers need to systematically examine the organization to determine what supports the new way and what hinders it. Companies that neglect to do that generally return to their old habits in six to ten months. “You need to scrub all procedures to make sure there are no magnets that will pull people back into their old ways,” he says.

“You need to cement into place new systems and behaviors that support the change effort and make sure everything is updated and in alignment with the change initiative. Anchoring the new approaches firmly into the corporate culture is important to prevent back sliding,” Armour concludes.

As you can see, implementing a change initiative that involves producing a major shift takes time, dedication, widespread support and cooperation. It also requires a willingness to move out of our comfort zones in order to embrace new approaches that can lead to positive improvements, growth and a stronger position in the marketplace. It’s critical to remember that change is ongoing and crucial to survival in today’s fast-changing, competitive environment. Don’t forget to embrace and start creating the future now.
With the Cardiac Safety Research Consortium, the FDA, and the Heart Rhythm Society, serving as co-sponsors, DIA welcomed approximately 100 participants to our conference on Cardiovascular Safety in Drug Development: State of the Art Assessments, presented April 14 and 15 at the L’Enfant Plaza Hotel in Washington, DC.

Phillip T. Sager, MD, FACC, FAHA, served as Program Chair. Dr. Sager currently serves as Chair of the Scientific Oversight Committee of the Cardiac Safety Research Consortium. The Cardiac Safety Research Consortium (CSRC) was launched in 2006 through an FDA Critical Path Initiative Memorandum of Understanding with Duke University to support research into the evaluation of cardiac safety of medical products. In 2009, Dr. Sager served as co-chair for DIA’s two-day workshop on Cardiovascular Safety & Development of Type 2 Diabetes Mellitus Medications, which was also collaboratively presented by DIA, the FDA and the CSRC.

The first session, CV Safety, Benefits & Drug Development: What is the Right Balance?, established the primary theme that ran like an undercurrent throughout this conference. It featured presentation of the payer, patient, and clinician perspectives on drug safety and benefit/risk assessment, and how to align these three perspectives. Other presentations explored how to appropriately determine benefit/risk and how much risk is acceptable. This session concluded with panel discussion of the question: Has “benefit” been overly de-prioritized over “safety” in determining benefit/risk with respect to public health?

Session two, Benefit/risk Determinations: Approaches & Impact on Drug Development, opened with a debate on benefit/risk analysis, proceeded through an evaluation of mathematical approaches to modeling benefit/risk, and concluded with discussion on how to determine if an individual signal is a public health issue or noise, and what sources to be most (and least) confident in while making that determination. Day one of this conference ended with a session on CV Safety: Blood Pressure, which featured both a debate and panel discussion: Debate on the question, “Is a ‘thorough BP’ assessment required for all drugs or only those with preclinical signals?”; and panel discussion on, “Do we need to do an outcome study if there is a BP signal?”

Day two’s opening focus was devoted to numerous critical QT Issues in Drug Development such as labeling implications and practices when there is a QT signal, phase 3 drug development when there is a QT signal, and statistical approaches to determining assay sensitivity in the absence of an active control; this session concluded with a mini-symposium on how to characterize the QT effects in early phase studies to permit replacement of the TQT study. The final session examined current and future initiatives surrounding CV Safety Data Evaluation & Long-term Safety Assessment.

Throughout the program, attendees received presentations delivered by numerous representatives of the FDA Center for Drug Evaluation & Research (CDER), such as Christine E. Garnett, PharmD; Mary Ross Southworth, PharmD; Ellis Unger, MD; Monica L. Fiszman MD, PhD; Lars Johannesen, MSc; Joanne Zhang, PhD, MS; and Norman Stockbridge, MD, PhD, who also served on the Scientific Program Committee with Peter Kowey, MD, FACC, Main Line Health System and Jefferson Medical College. In addition, Douglas C. Throckmorton, MD, (CDER) delivered a plenary lecture on “State of the Art and Regulatory Directions,” and Robert J. Temple, MD, (CDER), delivered a plenary lecture on “The Future of CV Safety & Drug Development” in the meeting’s closing session.

Each day also featured abstract presentations on emerging topics related to QT assessments and cardiac safety, including the validity of heart rate QT corrections, QT...
assessments when there is a heart rate increase, and discriminating changes in QT/QTc interval using dynamic beat-to-beat electrocardiogram analyses.

The preconference tutorial on April 13 provided An Introduction to the Clinical Assessment of QT Prolongation in Drug Development.

Dr. Sager delivered both the welcoming and closing remarks, and chaired several of these sessions. Afterwards, he shared these thoughts on cardiac safety in drug development and the importance of DIA’s collaborative conference on this topic.

You served as chair for DIA’s 2009 conference on cardiovascular safety in the development of type 2 diabetes mellitus medications. Why do you continue to serve as chair for DIA’s cardiovascular safety conferences?

Cardiovascular safety plays such a critical role in drug development, and the science continues to evolve so rapidly, that it’s been a real honor to be able to play a role in these programs because they focus on both education and building consensus, as well as facilitating groups of people who work together collaboratively to improve how we approach cardiovascular safety in drug development. For example, after the DIA Diabetes meeting, the Cardiac Safety Research Consortium held a ThinkTank to drive forward several collaborative efforts that came out of that DIA meeting.

The full title of our 2011 conference was “Cardiovascular Safety in Drug Development: State of the Art Assessments.” Would you briefly summarize advances in cardiac safety assessments that have emerged since this 2011 conference?

We’ve made huge strides in several areas, but the most noteworthy would certainly include: How we evaluate QT prolongation in drug development with new approaches and automated technologies that measure electrocardiographic intervals; more extensive use of pharmacokinetic/pharmacodynamic modeling (which has the potential to impact the thorough QT study when used in conjunction with other early clinical trial data); evaluating the impact of drugs on other electrocardiographic indices; assessing the potential safety aspects of increasing blood pressure; and how to appropriately weigh the risks of cardiovascular safety issues against the potential benefits of new chemical entities.

From your perspective as Program Chair, how did collaborating with the Cardiac Safety Research Consortium, the Heart Rhythm Society, and the FDA, benefit this program?

These programs are real collaborative efforts between the FDA, industry, and academia, and an essential part of these meetings is having these groups work together synergistically to consider the best approaches to how we optimize cardiovascular safety in drug development, develop creative and efficient ways to perform the necessary evaluations, and consider the numerous issues to make optimal benefit/risk assessments. A key part of these meetings is to identify areas for collaborative work to expand our scientific understanding of CV safety and drug development.

For readers who were unable to attend, would you briefly recap some of the topics discussed throughout this program?

This was an aggressive program agenda that covered many major topics related to cardiovascular safety in drug development. We started with an in-depth discussion on benefit/risk, how we deal with the risk of drugs as well as their benefit, and approaches to making optimal benefit/risk assessments. Of course, if a drug presents some risks, it is imperative to make sure that the benefits outweigh the risks, and how to assess this is an evolving science: It is critical that the benefit part of this equation is given appropriate balance along with risk identification, so that we don’t find ourselves in situations where we don’t move certain drugs forward because of some potential risk, even though they provide significant patient benefits. Identifying the patient populations in which the benefit/risk ratio is maximized is also critical. We also explored the current focus on safety and its potential impact on early drug development as well as any potential negative impact.

It’s become clear that increases in blood pressure can be potentially deleterious, particularly for drugs that are taken for a significant period of time and for patients who have significant cardiovascular risk factors. The meeting spent a good bit of time exploring this conundrum from both the preclinical and clinical perspectives, and what some of our options may be going forward in terms of evaluating blood pressure as a safety biomarker, from the technical side as well as the analysis of clinical significance. This effort will certainly be ongoing. Lastly, the use of automated ECG analysis technologies was explored, and this science seems to have matured to the point of delivering significant clinical and research impact.
DIA ANNOUNCES
2011-12 BOARD OF DIRECTORS

The 2011-12 DIA Board of Directors was announced at DIA 2011 in Chicago in June 2011. The Board of Directors is the steward of the DIA Mission & Vision and sets the overall strategy for DIA activities.

“Being an effective global community is a core component of DIA’s mission,” says Paul Pomerantz, DIA Worldwide Executive Director. “That’s why I want to personally recognize and thank each member of our Board of Directors comprised as it is of dedicated volunteers from around the world.”

The Board is elected by DIA members and has responsibility for setting DIA’s strategic direction, providing fiscal oversight, enhancing DIA’s public standing, and assuring the strength of DIA’s programs and services. Board members consist of senior professionals and thought leaders who are committed to DIA’s Mission and Core Values and who have experience in strategic planning and managing multidisciplinary responsibilities.

Each year, the Governance and Leadership Committee of the Board examines the makeup of DIA’s membership and tries to ensure that the nominations allow for a balanced representation of DIA’s constituents. In addition to experience with DIA, the Committee considers the demographic and geographic distribution, and diversity of candidates who may be elected to the Board.

Four Board members completed their terms in June 2011. DIA extends our deepest thanks to these four members for their distinguished service to the association:

Dr. Nandkumar K. Chodankar (CEO, Excel Industries Ltd, Mumbai, India). After graduating in Science from Goa, Nandu joined the University Department of Chemical Technology Mumbai as a National Scholar and completed his Bachelors and Masters degrees as well as his PhD in Chemical Technology. Nandu joined DIA as a volunteer in 1995 and continues to participate as a speaker at international DIA meetings. Most recently, he served as chairperson of the Advisory Council of India. Nandu has been a member of a number of Board committees and remains an active member of the Global Sourcing and Quality Risk Management SIACs.

Deborah Dolan, formerly Deborah Burns (Vice President, Key Accounts, AmerisourceBergen Corporation, PA). Debbie is a past chairperson of the Advisory Council of North America who served in this position from June 2004 through June 2008. She has also served on several Board committees. Debbie is an active member of several DIA SIACs including Global Sourcing, Regulatory Affairs, Document & Records Management, Evidence Based Medicine, and Electronic Regulatory Submissions, and has served as speaker at numerous DIA meetings.

Dr. Judith Glennie (Director, Strategic Health Technology Assessment, Janssen Inc., Canada). Judy has been involved with DIA since the mid 1990s and was elected to the Board in 2001. Judy has served on several Board committees and as a member of the Steering Committee for Canada. She is an active member of the Evidence Based Medicine SIAC and an advisor to the Canadian Program Committee,
and has served as speaker for numerous DIA meetings. Judy was called to public service via a Federal Cabinet appointment of the Patented Medicine Prices Review Board from 1995-1999. She has also served in the Ontario Ministry of Health and Long-Term Care-Drug Programs Branch, Health Canada’s Health Products and Foods Branch, and other public capacities.

**Dr. Jeffrey W. Sherman** (Chief Medical Officer and Executive Vice President, Development and Regulatory, Horizon Pharma, Inc. Northbrook, IL). Jeffrey is an Adjunct Assistant Professor of Medicine at the Northwestern University Feinberg School of Medicine and a Diplomat of the National Board of Medical Examiners and the American Board of Internal Medicine. Jeff received the DIA Outstanding Service Award in 2001 and served as Program Chairperson of the DIA Annual Meeting in 2008. In 2009, Jeff was elected DIA President and served as a result on the Executive Committee of the Board. Jeff has been a member of the Core Committee of the Investigator & Investigative Sites and Clinical Research SIACs, and has served as speaker for various DIA meetings.

Nominations for next year’s Board of Directors will soon be open on our website. Please visit www.diahome.org/nominations for nomination instructions and other information.

---

**2011-2012 Board of Directors**

Yves Juillet  
Ling Su  
Richard Day  
Minnie Baylor-Henry  

Michele Livesey  
Sandra Milligan  
Sandra L. Kweder  
Steve Caffè  
Truus Janse-de Hoog  

Thomas Kühlker  
John A. Roberts  
Per Spindler  
Jean A. Yager  
Larisa Nagra Singh  

Ning Xu  
Jennifer L. Riggins  
Beat Widler  
Tatsuo Kurokawa  
Sergio Guerrero
Patient Fellows' Reflections on DIA 2011

This year, DIA introduced a new Patient Fellowship Program at the 2011 Annual Meeting to enhance the participation of patient group representatives and to develop, strengthen, and support their collaborations with policy makers, health professionals, industry representatives and academia. Each of the fifteen participants was asked, "If you only had one thing that you could tell future Fellows, what would it be?" Some of the responses received are below.

- Fantastic experience – take advantage!
- Come prepared to advocate why including the patient voice in your clinical trials from the beginning is the key to successful recruitment, retention, and patient outcomes.
- Make the most of it and speak up!
- Come ready to listen and expand your knowledge; there is much to learn from those who are different from you; it is important to understand the other side.
- Attend as many sessions as possible and don’t miss the final breakfast wrap-up.
- Come ready to learn a lot. Enjoy your Fellow Advocates.
- Take advantage of this opportunity – you will learn many things about clinical research and drug development and gain many insights – figure out how to incorporate them into your day-to-day work.
- Stake out possible collaborations early on; if you are not familiar with the clinical trial process, be sure to do some research in advance to allow for a more valuable experience.
- Beginning with our October issue, future issues of the Global Forum will feature contributions from the participants in this year’s Patient Fellowship Program.
DIA’s robust eLearning program offers easy access to education anytime, anywhere. DIA eLearning is Internet-based courseware that can be accessed 24 hours a day, 7 days a week. Learners have access to the modules for one year from date of registration. This extended access allows learners to review module content at their leisure, and to start/stop at any time and begin where they left off. An added value to the DIA eLearning modules are continuing education credits. Learners must complete the module, evaluation and receive a passing score of 80% or better on the post-test to receive continuing education credits.

In addition to the DIA eLearning modules, DIA has also partnered with three other eLearning content organizations to extend the breadth and reach of DIA’s online learning portfolio. Most recently, DIA announced that it has partnered with Thomson Reuters IDRAC® to offer new educational opportunities in regulatory affairs to help learners navigate the ever-changing regulatory landscape.

“Our constituents represent a diverse group of global health care professionals all coming together to achieve their common professional aspirations essential to innovation in today’s health care environment,” says DIA Worldwide Executive Director, Paul Pomerantz. “IDRAC’s global reach, depth of analysis, and local expertise supports our commitment to providing in-depth knowledge of every regulation that could affect the discovery, development, and delivery of health care products around the world.” Together, DIA and IDRAC will deliver modules on topics such as European regulatory clinical trial requirements; orphan drugs in the US, Japan and Europe; introductions to the US, European and Japanese institutions and regulatory authorities; as well as the regulatory requirements for the submission of investigative new drug applications (INDs) in the US.

DIA also continues to partner with Kaplan EduNeering to offer educational offerings for biotechnology, pharmaceutical, academic and regulatory professionals to expand learners, professional skills and employment opportunities. Key topics include good clinical practices, selecting/managing contract research organizations, bioresearch monitoring, good manufacturing practices, change control and process validation.

The final partnership DIA has with Intellego, is to provide its Zenosis library of eLearning modules to professionals from around the world who are involved in the discovery, development, and life cycle management of pharmaceuticals, biotechnology, medical devices, and related health care products.

Intellego is an Internet-based learning-on-demand provider that incorporates the essential components of instructionally designed eLearning courses that ensure that the learning objectives of the individual are fully met. Their eLearning topics discuss variations to marketing authorization in Europe; registration of monoclonal antibodies; requirements for obtaining FDA approval for a generic product in the US and pharmacokinetics/pharmacodynamics in drug registration.

For more information on DIA’s eLearning portfolio or to register for any of these courses, please visit www.diahome.org/elearning.
DIA eLearning Modules

INFORMED CONSENT

This innovative eLearning module uses a detailed case study and examples taken from actual consent forms to provide an in-depth analysis of the key concepts of the informed consent process. Topics covered include the identification of situations that require consent, the proper methods of gaining consent, and the writing of consent forms and related documents for studies with different characteristics. The module also addresses unique situations that do not require consent, alternative methods of communicating consent information to different populations, and changes to informed consent under HIPAA.

Course Name: Informed Consent
Medical Communications eLearning Certificate Program

The DIA Medical Communications Certificate Program incorporates industry best practices into a systematic, comprehensive curriculum of nine modules addressing the key aspects of medical communications.

Course names:
- Crisis Management
- Database Management
- Literature Evaluation
- Literature Searching
- Medical Inquires
- Medical Writing
- Product Labeling
- Regulatory Issues
- Statistics for Medical Communications Professionals

CLINICAL INVESTIGATOR ELEARNING PROGRAM

DIA's Clinical Investigator eLearning Program provides a unique opportunity for clinical research professionals to learn the regulations, process, and best practices of conducting safe and effective clinical trials.

The eLearning program is made up of two modules: 1) Study Preparation and Initiation and 2) Conducting the Study. The eLearning program is an interactive case study that follows a fictitious clinical investigator and his study team through an entire clinical trial. At specific points throughout the story, you make decisions about what actions the characters should take. In this way, you can learn the concepts in context and in a way that greatly promotes learning and retention.

Course names:
- Clinical Investigator: Module 1 - Study Preparation and Initiation
- Clinical Investigator: Module 2 - Conducting The Study
With a collective 95+ years of service to DIA, seven long-term employees retired on June 30 during an afternoon gathering of cake and flowers and a bevy of good wishes and heartfelt gratitude at DIA Worldwide Headquarters in Horsham, PA. A formal retirement luncheon was held on July 14, but Worldwide Director, Paul Pomerantz, shared in the office festivities and spoke for the entire staff when he said, “What else can we say but thank you for your years of service and working hard at the Annual Meeting right up to the end.” DIA thanks them for all they have done for and been to the association and wishes them, luck, health, and happiness in their well deserved retirements.

MARY ANN CARNEY lives in North Wales and started with DIA in May 2002 as a part-timer; she was hired as a full-time employee later that year. For nine years, she worked as an Accounts Receivable Associate in the Finance Department. It will be hard not to see “the familiar faces that I am use to seeing every day for the past 9 years” says Mary Ann. But she is also looking forward to “spending time with my grandkids and travelling.”

LINDA CLER of Philadelphia, PA started with DIA in September 2004 and was the Administrative Assistant in the Marketing Department. She will miss seeing “the friends she has made over seven years everyday and plans to enjoy her retirement in a new home in Delaware with her first grandchild, a boy, due in October.”

NANCY KEISER of North Wales started with DIA in October, 1994 and describes her co-workers as “more like family than friends,” whether they are new hires or associates for over 17 years. During retirement, she plans on spending more time with her grandchildren, being more active in her community, reading for enjoyment (not proofing the annual meeting program!), and doing all the things around her home that have been neglected these many years. Nancy was the Marketing Department’s Production Manager.

FRAN KLAS has lived in Lafayette Hill for over 35 years and been with DIA as the Managing Editor in the Marketing Department since January, 2002. During her tenure, Fran oversaw the inception of the Global Forum and continued to grow it until her retirement. She will miss her colleagues, but has some hefty retirement plans including “training myself to get up later than 6:00am.” Others in her life also have plans for Fran: “My dog plans to be walked a great deal; she will not be happy sharing the house with me during the day, but she’ll have to adapt.”

SHERRIE LONGELLO started with DIA in November, 1998 and has commuted from Warminster since then. She will “miss working with the friends and colleagues I have met all over the world” as an Advertising and Graphic Designer in the Marketing Department. Sherrie plans on a well deserved relaxing summer before looking for freelance design work.

EILEEN ROTH is the longest tenured of our retirees. Starting with DIA in October, 1985, she served as Senior Manager for Worldwide Exhibits. Eileen makes her home in Abington and knows she will not be bored during retirement as she plans to “work part time in my husband’s tax business, make soup for my daughter’s restaurant, cook for my husband, babysit grandkids, expand the garden, redecorate the house, entertain friends, learn to knit, take classes – whatever comes along.”

JEAN ZANE came to DIA 12 years ago, and started in May 1999 as Manager of Customer Service for the Horsham Office. Originating from Omaha, Nebraska, Jean will “miss my colleagues at DIA. They have been my ‘work family’ and such an important part of my life.” She plans on spending a lot of time in retirement catching up on her leisure reading.
In response to the announcement of the recent passing of one of DIA's founding fathers, Thomas W. Teal (Cdr., USN Ret.), current and former members from many corners of our global network shared their own reflections on Mr. Teal. Several of these responses are shared below.

Nandkumar K. Chodankar: Former Chair, DIA Advisory Council of India

This is indeed sad news. Though I have never personally met Thomas W. Teal, I have great respect and reverence for him. It was his great idea that made DIA what it is today.

Dr. Tatsuo Kurokawa: Chair, DIA Advisory Council of Japan

Japan’s internationalization and improvement in its pharmaceutical and regulatory activities very much depends on DIA’s generous contribution. Mr. Thomas W. Teal had extended his kind thoughts on Japan with great provision and infinite patience. I wish to express my deepest condolences, which I am sure will be shared by all DIA members, friends, and all people who know DIA in Japan.

Judith L. Glennie: Former Director, DIA Board of Directors

I am very sorry to hear this sad news. I met Mr. Teal a few times in my early days of involvement in DIA. I was very much inspired by his vision and dedication to DIA. My deepest sympathies to Carol and her family. He will be greatly missed.

Dr. Ling Su: DIA President-elect; Former Chair, DIA Advisory Council of China

My deepest sympathies to Carol and her family, and to the all DIA’ers – staff and volunteers and members – who have benefited from his vision.
In September 2010, FDA issued an interesting and partly surprising new draft guidance: “Safety Reporting Requirements for INDs and BA/BE Studies,” which went into effect March 28, 2011, but with a “grace period” for implementation till September 28, 2011.

The guidance is the long-awaited resolution to all the debates around the rule proposed in 2003 dubbed “The Tome.” But it is only a partial answer, since it is addressing the premarketing half of the Tome; an update for the postmarketing half can be expected some time in the future.

The interesting part of the new guidance is that it seems to reflect quite a change in focus within the FDA from compliance to interpretation and medical judgment. The targeted change is to reduce “noise” and enhance the “message.” In contrast to past practice, FDA now explicitly requests sponsors to evaluate the data, and only submit to FDA what the sponsor deems of interest (ie, is thought to be related to the product).

The new guidance is a very welcome and reasonable document that stimulates safety departments and sponsors to focus on the right thing: ie, analyzing safety profiles of products as they emerge and adequately communicate and manage potential new safety signals and findings. Although targeted to allow further harmonization, unfortunately the new guidance poses some new challenges, especially for those working in a global setting - which is the case for most of us nowadays. It may even trigger reintroduction of some inconsistencies or duplicative efforts to satisfy regulations in different regions. Below, those areas of the new guidance of strongest impact on safety operations are highlighted, and associated potential challenges discussed. Some suggestions on how to best address these challenges are provided.

Causality
Probably the most important and remarkable part of this new guidance is the new interpretation of “associated with the use of the drug.” The FDA is moving from the “cannot be excluded” as initially proposed in the Tome to the other extreme of “reasonable possibility”, defined as requiring some evidence. This is certainly helpful for lowering the administrative expedited reporting burden on non-value-added information. However, this new specification of what constitutes a related and thus expeditable event is slightly beyond international standards. Whereas one can argue that the ICH “reasonable causal relationship” (“...there are facts (evidence) or arguments to suggest a causal relationship”) is consistent with what FDA is heading for, the WHO causality definitions clearly drives towards a more conservative assessment. WHO is inconsistent with FDA current proposal in that it defines possibly related with an “escape”: “[…] but which could also be explained by concurrent disease or other drugs or chemicals.” The new guidance considers such cases as not expeditable. Current practice with most companies is more in line with the WHO definition and errs on the side of caution. A case with some evidence for a causal role for both drug and alternative factors will generally be assessed as related and thus expeditable. De-harmonizing into separate assessments for causality and/or expeditability for EU vs. US does not seem a good idea for more than one reason. Therefore, those of us working in a global environment and having to continue to meet ex-US requirements probably should not take the FDA suggestion to an extreme. Instead, a conservative interpretation of the new FDA definitions and less conservative of current WHO definition with some documentation in the company procedures may be the way to go. This means an even more delicate balancing act for those having to make the “unlikely/possibly related” judgment call.

Excluding Endpoints
The FDA now calls for excluding from expedited reporting those events that are also study endpoints, especially in studies on disease related mortality or major morbidity. This certainly is a helpful specification to the IND regulations, and its implementation can be relatively straightforward. This is
already common practice for some companies. The protocol needs to specify which events are to be excluded from SAE reporting. Since FDA still wants expediting of such cases “in unusual cases,” investigators have to be educated to still report them as SAEs if they judge the event to be atypical and the drug to have contributed.

**Excluding Co-morbidity**

Additionally, the new guidance indicates FDA no longer wants to receive individual expedited reports for other serious events that are likely consequences of underlying disease or common for the study population. Although this also makes a lot of sense, this requirement is trickier than the exclusion of study endpoints. Many of our common AEs behave like concurrent diseases occurring with a certain background incidence. Medical judgment is needed to distinguish “background noise” for that population from drug-induced noise. Simply excluding such cases from SAE reporting would not be appropriate, since the new guidance requires expedited reporting on increased incidences or other signals from the aggregate review of such events. Therefore, sponsors still have to gather, and thus investigators report, these co-morbidity events. The challenge then is to exclude such cases, received as SAEs from expediting, while remaining compliant with US and ex-US regulatory requirements. There are various options to cover this, unfortunately none of them really fully satisfactory. Usually events related to pre-existing disease would be considered unlikely related to drug, and this should not be an issue for the sponsor assessment. However, investigators’ causality assessments are not always consistent and logical. FDA states in this new rule that a sponsor can overrule investigator causality. However, this is not consistent with current safety practice of “most conservative assessment prevails for expedited reporting” and is not necessarily acceptable ex-US. An option may be to provide the investigators with a list of terms likely to be occurring with the disease or population, for example in the protocol or Investigator’s Brochure. This however may be problematic since it might cross the line of independent investigator assessment and cause confusion resulting in assumptions that such events don’t need to be reported at all. Also, an all-inclusive list of potential co-morbid situations is hard to arrive at, and may prevent reporting of relevant “unusual” events that happen to be included in the list. An alternative approach may be to call such co-morbid situations “expected” events, eg, in Investigator Brochure, and thus disqualify them for expediting. However, this stretches the definition of “expectedness” beyond its regulatory meaning and is most likely not acceptable for all authorities. Therefore the most reasonable way to address this requirement seems education prior to trial initiation, eg, through clear instructions at investigator meetings about these events.

**Expediting of Data from Other Sources or Aggregate Review**

The requirement to provide findings from aggregate review and data from other sources (eg, clinical database, epidemiology) as 15-day reports seems reasonable. However, most companies do not have existing procedures or systems to do so. The safety databases used for expedited reporting of individual cases aren’t geared to do something similar for aggregate data, and usually don’t include data from “other sources.”

Also, the MedWatch or E2B format is not necessarily suitable for reporting such aggregate findings expeditiously to FDA.

Safety organizations - if they have not done so - have to arrange for ongoing review of aggregate safety data from various sources, and add processes to that for determining what constitutes an “expeditable safety finding/signal” and for the actual submission of such findings as 15-day reports.

**No Follow-up Reports to Investigators**

The guidance’s suggestion not to provide investigators with routine follow-up reports is a great one and will save both companies and investigators quite some administrative burden. The interpretation of what follow-up information qualifies for reporting will differ significantly between companies. The FDA suggested “significant change that will impact the care of subjects or the general conduct of the study” is hard to imagine since rarely any initial report sent as Investigator Notification meets that criterion. It may be a reasonable approach to limit sending follow-up reports to investigators for new information that changes the event (ie, change in diagnosis), or the interpretation of the event (causality) in reports they have previously received.

This requirement furthers the existing inconsistent requirements for investigator reporting across the world, but specifically between EU and US. Now ex-US investigators may see more reports than the US investigators. Unfortunately the current FDA guidance does
It is hoped and expected that FDA’s pending Postmarketing revision will carry the same spirit as this document and allow us to further focus on analysis rather than administration of safety data.

References:

Mariette Boerstoel-Streefland, MD, MBA, MSc(epi) is Chief Safety Officer, VP Global Drug Safety, Forest Laboratories Inc. Readers can contact her at mariette.boerstoel@frx.com.

not allow replacing the 15-day investigator reporting with periodic line listings as is allowed by the EU Clinical Trial Directive.

Investigator Brochure
Additional details are provided on the inclusion of relevant safety data in the Investigator Brochure. It prescribes the inclusion of a list of events that have been observed and are potentially causally related (i.e., the list of expected events). In addition, a table describing events expected to occur based on the pharmacological profile or class of drugs is now requested (these events are to be considered “unexpected” until actually observed).

Un-blinding of All Expedited Reports
The guidance now clearly states FDA expects cases to be unblinded before expediting, something that was not explicitly stated before. For most companies this should not be much of an issue since this is required by other authorities already. In those companies that are not yet used to routine unblinding of expedited cases, some of the traditional sentiment (and angst) surrounding a potential impact on study integrity and power may trigger additional discussions with clinical, statistics and the like. Clear procedures need to be in place to cover this process and if considered useful, a firewall can be established between those involved with the conduct of the study and the results of this unblinding.

ASIME
Not much is changing for the Analysis of Similar Events requirement (ASIME). Some were hoping that this rather unique US requirement would be abandoned. Standardized or consistent search criteria for “similar events” are lacking, and thus the interpretation on how narrow or broad to search varies greatly between companies. This guidance does not add specifics, so companies should probably keep their existing practices.

Conclusion
The new FDA guidance, issued as draft in September 2010, and final per March 2011 is a very welcome document with its general direction towards making expedited safety reporting more meaningful. There are a number of challenging aspects though, which seem to be manageable with some revisions of in-house processes and definitions. It especially forces us to think about causality assessments, the exclusion of study endpoints and events related to underlying disease from expediting to FDA. However, the biggest challenge (as always in drug safety) is to satisfy the various regulations and regulators around the world, while running an efficient organization with available resources to monitor and address potential safety issues. It is unfortunate that we are still being distracted by dealing with non-value-added administrative and regulatory hurdles. The best approach is to keep a pragmatic mind, and take the middle road, trying to maintain a “compliant one size fits all” for the routine safety reporting.

The above is not an all-inclusive review of the new guidance; one should read and re-read the document itself to understand the full implication for one’s specific area/company.
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 topics of pharmacovigilance and drug safety, the special focus of this issue, include:

**Australia - Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Medicines Jul-2003, as Amended 01-Jun-2011**

This guideline has been developed for sponsors to report adverse reactions to both listed and registered medicines regulated by the Drug Safety and Evaluation Branch (DSEB) of the Therapeutic Goods Administration (TGA). The Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Medicines (July 2003) has been amended to include listed medicine pharmacovigilance requirements. This new version replaces the advice provided in any previous documents relating to pharmacovigilance requirements for either listed or registered medicines including "Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch, Jul-2003" and "Australian Regulatory Guidelines for Complementary Medicines". All sponsors are expected to comply with the requirements set out in this document.


This document provides the 2011 work plan for the Pharmacovigilance Inspectors Working Group. The Group’s activities revolve around the harmonization and coordination of pharmacovigilance-related activities at community level. This document covers the following topics: - Meetings - Inspections conducted in support of the centralized procedure - Harmonization topics - Pharmacovigilance topics - Collaboration with the European Commission - Liaison with other groups - International Cooperation.


This document provides information on the second stakeholder forum on the implementation of the new pharmacovigilance legislation of 2010 held at the European Medicines Agency on 17-Jun-2011. The aim of this forum is to raise awareness of the requirements of the new legislation and to advertise and encourage the exchange of ideas, concerns and opinions. This document provides the following elements on this workshop: Agenda Report on the Workshop List of

*Update to Guidance on Pharmacovigilance - Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch, Jul-2003 and Australian Regulatory Guidelines for Complementary Medicines.* All sponsors are expected to comply with the requirements set out in this document.


This document provides the 2011 work plan for the Pharmacovigilance Inspectors Working Group. The Group’s activities revolve around the harmonization and coordination of pharmacovigilance-related activities at community level. This document covers the following topics: - Meetings - Inspections conducted in support of the centralized procedure - Harmonization topics - Pharmacovigilance topics - Collaboration with the European Commission - Liaison with other groups - International Cooperation.


This document provides information on the second stakeholder forum on the implementation of the new pharmacovigilance legislation of 2010 held at the European Medicines Agency on 17-Jun-2011. The aim of this forum is to raise awareness of the requirements of the new legislation and to advertise and encourage the exchange of ideas, concerns and opinions. This document provides the following elements on this workshop: Agenda Report on the Workshop List of

The European Medicines Agency has hosted a second workshop on the changes to the safety monitoring of medicines in Europe, which gave the opportunity to patients, consumer groups, health care professionals and the pharmaceutical industry to express their expectations. The new pharmacovigilance legislation was adopted in the European Union in December 2010 with the objective to save lives by strengthening the European-wide system for monitoring the safety of medicines. The outcome of the day’s discussions will be used to guide the implementation of the legislation, which is scheduled to come into force in July 2012.

The CHMP Pharmacovigilance Working Party (PhVWP) held its June 2011 plenary meeting on 20/22-Jun-2011. During this meeting, 4 topics on safety concerns were discussed: - Beta-blockers for ophthalmic use – Risk of systemic adverse reactions - GEMCITABINE ACTAVIS – Risk of adverse reactions due to increased alcohol concentration after reconstitution error - Hydrochlorothiazide – Use during breast-feeding. - Testosterone 10% for topical use – Risk of virilisation in children after exposure through interpersonal skin contact.

This BfArM and PEI Pharmacovigilance Bulletin, 2nd Issue (Jun-2011) covers the following topics: - Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN): product information requirements. - Risk of lactacidosis with metformin. - Hepatotoxicity associated with endothelin receptor antagonists (ERAs) - Increased risk of febrile seizure after measles-mumps-rubella and varicella vaccination - Basics of pharmacovigilance (Part III): risk assessment procedure in the European Union - BfArM and PEI news - List of current pharmacovigilance news (risk information, Dear Doctor Letters, Red Hand Letters) issued from 01-Apr-2011 to 16-May-2011 on the BfArM or PEI websites and available in IDRAC.

Peru - Over 4,000 Adverse Drug Reactions were Reported in 2010, 01-Jun-2011
The Peruvian general directorate of medicines supplies and drugs (DIGEMID) announced 4,600 adverse drug reactions were reported in 2010, among which the most common events were edema, headache and swelling in different parts of the body. DIGEMID professes antibiotics, painkillers and anti-inflammatory medicines were the most common source of adverse drug reactions in 2010. DIGEMID pointed out that under no circumstances should any medicinal product be administered without prescription. Patients should only take the dosage prescribed by doctors, follow the whole pharmacological treatment, let their doctors know if they are using other medicines and report to them any adverse event that may set in. DIGEMID urged practitioners to report any drug reaction to the Peruvian pharmacovigilance system so that the Ministry of Health’s institution can take measures to increase control in the country and guarantee population’s safety by modifying indications and warnings of medicinal products.

Portugal - INFARMED Pharmacovigilance Bulletin Volume 15 - No. 2, 2nd Quarter 2011 (Portuguese and English Versions)
This Bulletin published by the Infarmed deals with pharmacovigilance issues during the 2nd Quarter 2011.
Scott Fedor’s life changed in the shadow of a second in July 2009. He plunged into Coldwater Lake a successful, physically fit, happily married 33-year-old executive. He emerged a quadriplegic whose life would be redirected and redefined by his injury.

Scott’s story is all too familiar to people with spinal cord injuries: a long hospital stay, slow rehabilitation, setbacks, relapses, frustration, fear, depression, anxiety.

Despite the challenges he continues to face, Scott remains hopeful. Much of that hope, he says, comes from his experience with clinical trials.

Starting Over
After his accident and a two-week hospital stay in Michigan, Scott was flown to MetroHealth Medical Center in Cleveland which he calls the “epicenter of spinal cord research” in Ohio.

It was during his stay at Metro, several months into his recovery, that Scott met another quadriplegic who was demonstrating a new technology called a spinal cough assist system. The device, which was in clinical trials, is designed to generate a cough in spinal cord patients whose abdominal muscles are paralyzed.

The inability to cough is a major problem for patients with spinal injuries. Because they are unable to clear secretions from their lungs, patients must be suctioned via a trach tube. The need for suctioning dramatically limits their independence – they must always travel with a suction kit and someone trained to use it – and presents a potentially life-threatening risk.

Pneumonia is the second leading cause of death among quadriplegics.

At the time, Scott’s lungs, which were badly damaged during his accident, were being suctioned as many as six times a day. Still, he says, the trial technology didn’t impress him. He didn’t think the woman performing the demonstration appeared terribly healthy and she wasn’t using the device very effectively.

Scott desperately wanted to live his life without being suctioned and wanted the trach tube removed, as it posed an infection risk. What’s more, he knew from personal experience the potential benefits of implanted devices. Months earlier he’d had a diaphragm pacing system implanted that had enabled him to breathe without a ventilator. Still, he wasn’t convinced this new technology held much promise.

“What I’d read on paper about the device wasn’t what I saw during the demonstration that day. I remember asking myself, ‘Is this worth having my spine cut open for?’ ” Scott told his doctors he was still undecided.

A few weeks later, Scott had reason to reconsider his decision when his doctors introduced him to a second patient who had been implanted with the cough assist system. The young man, whose story and injury mirrored Scott’s, “looked to be in really good health,” Scott recalls. “He came in and showed me this really forceful cough. It was night and day between him and the demonstration with the other woman.”

Scott’s interest was piqued. “I started asking a lot of questions,” he says. Researchers noted that there were a number of explanations that might account for the discrepancy in the two patients’ coughs, including the device setting, the patients’ age and the extent of muscle atrophy.

“Until you have the surgery and test the device a few months after it’s implanted, there’s really no way of knowing how your body is going to react to it,” Scott says.

Scott faced a tough decision. Only 13 people had been implanted with the device so far. Three of them were dead, one as the result of a septic reaction from an infection due to not keeping the implant site clean.

Weighing the Risks
Scott considered the risks. He’d have to be on a ventilator during the six-hour surgery, an inherently risky proposition for a cord patient. There was a danger Scott’s muscles might atrophy during the procedure.
and he’d spend the rest of his life on a ventilator. To complicate matters, researchers were preparing to test a new version of the technology. If Scott wanted to participate in the trial, he would have to agree to remain anesthetized for an extra hour so doctors could test the wiring that would be used in the next generation of the device.

Finally, Scott says, he had to wrestle with a deeply personal fear. “I was nervous about becoming the bionic man,” he says. “I still had a strong belief that my body would repair itself. I didn’t want to turn myself into a part robot. I wanted my body to remain as whole and uncompromised as possible.”

As time went by, Scott’s abdominal muscles weakened and his lungs had to be suctioned with increasing frequency. Ultimately, Scott decided the independence and enhanced quality of life the cough assist system promised justified the risks.

“I decided: if I can do things now to help give me more independence and help restore me, why not? Yes, there are risks, but my life expectancy goes up if I can clear my secretions.”

In September 2010, Scott underwent a grueling surgery that lasted nearly eight hours. A surgeon made an incision in the middle of his back and drilled into his T9, T11 and L1 vertebrae. A small electrode was placed on the dura mater surrounding his spinal cord and connected via a wire to a receiver on Scott’s abdominal muscles. To stimulate a cough, an external receiver that was not attached to the body would be held against Scott’s abdomen where the internal receiver was located. Pushing a button on the external receiver would send a charge to the spinal cord nerves that would trigger the abdominal muscles to contract, forcing a cough.

The surgery went well and Scott was taken off the ventilator without incident, but he had to wait several weeks to learn whether or not the surgery had worked.

Scott can still remember the day when he was finally allowed to test the device. “I was making jokes, but I was a little apprehensive,” he says. “The doctors were telling me I’d have to learn to time the cough with the jolt. Since I didn’t know what it was going to feel like, I wasn’t sure what that was going to mean.”

His initial reaction upon being shocked was relief: it didn’t hurt. Still, he says the sensation was strange. Because he didn’t have his timing down, it felt “like swallowing a really big hiccup.” After a few tries, Scott’s timing improved and he was able to produce a very productive cough.

“To me it was a really powerful sound that I hadn’t made in a long time,” he recalls.

After a few weeks of practice, Scott began to experience the benefits of the surgery. Soon he was able to clear his secretions and, by December 2010, he was able to have his trach removed.

“That was a life changer,” he says. “A big hope of mine was realized.”

The Road Ahead

Today, nearly a year after the surgery, Scott continues to do well. He regularly demonstrates the cough assist device for other spinal cord patients and says he continues to discover new, secondary benefits. He recently learned to use it to stimulate a sneeze.

His experience has been so positive he hopes to be selected for a second trial. Doctors at Metro hope eventually to conduct a trial of a functional electronic stimulation (FES) bicep implant. Scott is undergoing preliminary assessments and hopes he will be a candidate for the procedure when the time comes.

Although he’s working on developing a new career as a motivational speaker, Scott’s not a pollyanna. He’s frank about what his injury has cost him: his physical body, marriage and financial independence.

Still, he’s optimistic about the future. He knows that trials have risks and that they often don’t realize their objectives. But, he’s willing to keep trying. “I think there’s a lot to be said about having a positive mental attitude,” he says. “In a trial you have to go into it saying, ‘This is a chance – if it works – to get some independence back in my life.’”

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.”
DIA Members on the Move

DIA is committed to improving the professional performance of our members and volunteers through our educational and networking forums. Please join us in congratulating the following DIA members for their recent professional accomplishments:

David Hardison was appointed Managing Director of Health Sciences at Recombinant. Prior to this appointment, David served as Vice President & Chief Health Scientist at Science Applications International Corporation. He earned his PhD in Biostatistics with minors in Epidemiology & Data Management for the University of North Carolina School of Public Health, and BS in Mathematics & Computer Science from Vanderbilt University, graduating Magna Cum Laude with High Honors in Mathematics. David has also served as Chairman of the Board for the Clinical Data Interchange Standards Consortium (CDISC).

Barbara Godlew was appointed Director, Huron Consulting Group, for clinical research management and disclosure for life sciences, academic medical center, and healthcare clients. Barbara previously served as president and founder of The FAIRE Company. Barbara earned her BA from Colorado State University, holds a Medical Writing Certificate from the Graham School, University of Chicago, and is also a registered nurse. Barbara serves as chair of the DIA Clinical Trial Disclosure SIAC, and is also a member of the Regulatory Affairs Professionals Society and the American Academy of Neurology.

ON THE MOVE? LET US KNOW

If you’re an active DIA member and would like to share your professional or career news with other members in our Global Forum, please send your announcement (and high-resolution digital photograph, if you have one) to Chris.Slawecki@diahome.org. All submissions are subject to DIA editorial review and approval. Please remember to keep your DIA member profile current by logging into “My DIA” and updating your contact information to reflect your new job title, employer, or email address, too.

Maryann Szabo, RN, BS, received the Tribute to Women and Industry (TWIN) Award at the 37th Annual TWIN Awards Dinner. Maryann serves as Director, US Affiliate Regional Monitoring Network, for Roche’s US Affiliate. In 2010, Maryann was named by PharmaVOICE as one of “100 of the Most Inspiring People” in pharmaceuticals. Maryann earned her RN from Passaic County Community College (NJ) and her BS in Health Care Administration from St. Joseph's College (ME). She is also a member of the Association of Clinical Research Professionals and the NJ State Nurses Association.

Peter Lassoff was appointed Practice Leader of the EU Pharmaceutical Regulatory & Quality practice for the Consulting at Quintiles European team. He served as Vice President of Consulting in Europe for PAREXEL prior to this appointment. Peter earned his PharmD from the University of Southern California School of Pharmacy.

Michael D. Webb was appointed President & CEO, and also appointed to the Board of Directors, of Allegro Diagnostics, Inc. Michael previously served as founder, President, and CEO of Anchor Therapeutics, Inc. He is also Executive Chairman of Vertify, Inc., and has served as Chairman of the Massachusetts Biotechnology Council. Michael holds his MBA from Northwestern University, his Masters in International Relations from Sussex University, and his BA/BS in Biochemistry and Economics from the University of Kansas.

Peter Lassoff was appointed Practice Leader of the EU Pharmaceutical Regulatory & Quality practice for the Consulting at Quintiles European team. He served as Vice President of Consulting in Europe for PAREXEL prior to this appointment. Peter earned his PharmD from the University of Southern California School of Pharmacy.

If you’re an active DIA member and would like to share your professional or career news with other members in our Global Forum, please send your announcement (and high-resolution digital photograph, if you have one) to Chris.Slawecki@diahome.org. All submissions are subject to DIA editorial review and approval. Please remember to keep your DIA member profile current by logging into “My DIA” and updating your contact information to reflect your new job title, employer, or email address, too.

Maryann Szabo, RN, BS, received the Tribute to Women and Industry (TWIN) Award at the 37th Annual TWIN Awards Dinner. Maryann serves as Director, US Affiliate Regional Monitoring Network, for Roche’s US Affiliate. In 2010, Maryann was named by PharmaVOICE as one of “100 of the Most Inspiring People” in pharmaceuticals. Maryann earned her RN from Passaic County Community College (NJ) and her BS in Health Care Administration from St. Joseph's College (ME). She is also a member of the Association of Clinical Research Professionals and the NJ State Nurses Association.

Michael D. Webb was appointed President & CEO, and also appointed to the Board of Directors, of Allegro Diagnostics, Inc. Michael previously served as founder, President, and CEO of Anchor Therapeutics, Inc. He is also Executive Chairman of Vertify, Inc., and has served as Chairman of the Massachusetts Biotechnology Council. Michael holds his MBA from Northwestern University, his Masters in International Relations from Sussex University, and his BA/BS in Biochemistry and Economics from the University of Kansas.
Clinical Reporting and Visualization Made Simple

info@comprehend.com
www.comprehend.com
877-201-3560

Connecting clients with thousands of clinical research monitors around the globe.
P: 610.862.0909
F: 610.862.0912
www.monitorforhire.com
610.233.3300
www.myoderm.com

Myoderm CentralSource: Standardization of commercial medications across your clinical sites with our central sourcing and site distribution.
610.233.3300
www.myoderm.com

Queensland Clinical Trials Network Inc.
Level 3, 88 Jephson Street
Toowong, Queensland 4066
Australia
Phone: +61 7 3331 3999
Fax: +61 7 3870 9101
Email: marketing@qctn.com.au
www.qctn.com.au

The Medical Research Network (MRN) is a unique clinical trial support organisation offering nursing focused patient recruitment & retention solutions globally for clinical trials.
+44 (0) 7764 965 039
stuart.redding@themrn.co.uk

Full service
Complex study specialists
On time & within budget

We do it right the first time.
70 Church Street • Flemington • Nj • 08822
+1-908.788.1779 • www.beardsworth.com

AAHRPP - Full Accreditation IRB Services
Here to Protect What’s Important in Life
Phone: 913-385-1414
Fax: 913-385-9999
www.mlirb.com

Norwich
Your comprehensive solution for all stages of the product lifecycle
www.NorwichPharma.com

PDR Network

Virtual Clinical Solutions
Providing Secure, Cost-Efficient and Timely Virtual Training For Investigational Sites
615-891-5430
www.virtualclinical.com

Web Wise Learning
Traditional and Interactive Performance Support Solutions
2626 E 82nd St #330
Bloomington MN 55425
ph 952.883.0800
fax 952.854.1685
www.webwiselarning.com

SNBL Clinical Pharmacology Center
Managing Complexity. Enabling Results.
• Full-Service CRO
• Phase III/IIA Clinical Research Facility
• 96 Bed Unit
• Multitherapeutic Indications
• On Site Clinical Laboratory
• Located in Baltimore, MD
1-800-690-9110 BD@SNBL-CPC.COM
www.snbl-cpc.com

AAHRPP - Full Accreditation IRB Services
Here to Protect What’s Important in Life
Phone: 913-385-1414
Fax: 913-385-9999
www.mlirb.com

Norwich
Your comprehensive solution for all stages of the product lifecycle
www.NorwichPharma.com

PDR Network

Virtual Clinical Solutions
Providing Secure, Cost-Efficient and Timely Virtual Training For Investigational Sites
615-891-5430
www.virtualclinical.com

Web Wise Learning
Traditional and Interactive Performance Support Solutions
2626 E 82nd St #330
Bloomington MN 55425
ph 952.883.0800
fax 952.854.1685
www.webwiselarning.com

SNBL Clinical Pharmacology Center
Managing Complexity. Enabling Results.
• Full-Service CRO
• Phase III/IIA Clinical Research Facility
• 96 Bed Unit
• Multitherapeutic Indications
• On Site Clinical Laboratory
• Located in Baltimore, MD
1-800-690-9110 BD@SNBL-CPC.COM
www.snbl-cpc.com

AAHRPP - Full Accreditation IRB Services
Here to Protect What’s Important in Life
Phone: 913-385-1414
Fax: 913-385-9999
www.mlirb.com

Norwich
Your comprehensive solution for all stages of the product lifecycle
www.NorwichPharma.com

PDR Network

Virtual Clinical Solutions
Providing Secure, Cost-Efficient and Timely Virtual Training For Investigational Sites
615-891-5430
www.virtualclinical.com

Web Wise Learning
Traditional and Interactive Performance Support Solutions
2626 E 82nd St #330
Bloomington MN 55425
ph 952.883.0800
fax 952.854.1685
www.webwiselarning.com

SNBL Clinical Pharmacology Center
Managing Complexity. Enabling Results.
• Full-Service CRO
• Phase III/IIA Clinical Research Facility
• 96 Bed Unit
• Multitherapeutic Indications
• On Site Clinical Laboratory
• Located in Baltimore, MD
1-800-690-9110 BD@SNBL-CPC.COM
www.snbl-cpc.com
One partner.
Four product-critical services.
Complete peace of mind.

Trust our industry experts to support your products with seamless customer service and full regulatory compliance. Individual or integrated solutions available.

ddnmedicalaffairs.com 414.434.8400

Medical Affairs
A Dohmen Company
Cut time & cost with Spaulding iQ™ Electrocardiograph

- No equipment rental or setup fees
- Biometric voice print technology virtually eliminates costly demographic errors and time-consuming reconciliation
- Store up to 5 minutes of 12-lead ECG data instead of just 10 seconds
- Small, lightweight unit minimizes shipping expenses
- Automated data upload via secured internet simplifies data transmission
- 12-lead unconfirmed report immediately available with automated interpretation
- Board-certified cardiologist over-read within 24 hours

Scan to view our DIA demo of the Spaulding IQ on Facebook or for more information, visit spauldingclinical.com