GLOBAL FORUM

DRIVING IDEAS TO ACTION

RARE DISEASES

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DIA DEVELOP INNOVATE ADVANCE

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DIA *Global Forum* provides a multidisciplinary, neutral forum for communicating information related to drug development and life cycle 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 electronically six times a year.

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Rare Diseases, Genomic Medicine and Progress

Barbara Lopez Kunz
Global Chief Executive
DIA

Over the past decade, we have seen a transformation in the health care community's approach to rare diseases, and progress is intimately entwined with our evolving understanding of genomic medicine. This revolutionary science tells us that approximately 80% of known rare diseases are genetic in nature and that relatively few of the millions of people suffering globally from a rare disease are effectively treated by existing therapies. Furthermore, the most significant population impacted by these deadly diseases is our children, most of whom, when afflicted with a rare disease, have a life expectancy in the single digits. Read more about the need for pediatric research in several Special Populations articles and the editorial, "Progress on Behalf of Children," in the recent issue (September 2016) of DIA's peer-reviewed scientific journal, *Therapeutic Innovation & Regulatory Science (TIRS)*.

How do we harvest the rich pool of genetic and related patient data that could be instrumental in developing therapies and finding cures for rare diseases? The challenges are many but certainly not insurmountable with open collaboration, the core idea that led to the founding of DIA 52 years ago. The need to openly communicate across the entire health care ecosystem and to engage the patient community with those stakeholders who develop, regulate, administer, and pay for therapies is critical. This issue of the *Global Forum* takes a close look at rare disease and unmet medical needs from a comprehensive perspective - global in nature, diverse in discussion areas - focused on accelerating the care and finding cures for those most in need.

And the need is great: to invest in and support fundamental research; to educate every stakeholder contributing to health care product development and life cycle management on ways to improve scientific and operational processes; to respect confidentiality and privacy while sharing data from clinical trials and patient registries, electronic health records and other sources. I am sure you could add to this list.

DIA's unique global forum enables you to openly share your knowledge, ideas and, more importantly, work with your peers to transform these ideas into action all around the world. This fall there are many opportunities for you to contribute to this forum: Our *Clinical Forum for Operational Excellence* in Dusseldorf, Germany; our *Canadian Annual Meeting 2016* and annual *Biosimilars* and *Combination Product* programs in North America; our *China Drug Discovery Innovation Conference*; our *Cardiac Safety Workshop* in Japan; and many more. We are particularly looking forward to hosting our *ICH/DIA Joint Tokyo Workshop* just a few days after the ICH Assembly holds their biannual meeting in Osaka, and convening our *13th DIA Japan Annual Meeting 2016* the very next day.

No matter where you live or work, as a DIA member you can access our eLearning and other online educational programs, connect with global colleagues through our online Communities, and contribute to and learn from our *TIRS* scientific journal and our *Global Forum*, all through our website.

The great scientist Charles Darwin once said, "It is the long history of humankind (and animal kind, too) that those who learned to collaborate and improvise most effectively have prevailed." It is clear that science will eventually help us discover and deliver therapies for even the rarest disease, so long as we all work together toward our common goal. It is up to us to lead the way.

Rare Diseases, the Voice of the Patient, Evidence Generation and Conditional Approval

Alberto Grignolo, PhD
Deputy Editor
Global Forum

The Special Section of this issue of Global Forum is on Rare Diseases, and it is thought-provoking on many levels.

Firstly, the attention being paid by industry and regulators to conditions that afflict relatively modest numbers of patients is commendable, is growing and is a testament to the success of orphan product initiatives that were born in the 1980s. At the beginning it was not clear that this would attract so much interest and become the heart-warming global phenomenon that it is today.

Second, the long-standing focus on rare diseases has raised important questions about the role (the "voice," the passionate advocacy) of suffering patients, families and caregivers during the development of suitable therapies; about how to generate clinical evidence to support regulatory decisions when so few patients are available for study and the endpoints may be "surrogate"; about the role of "real-world evidence" to supplement clinical trials data; about securing regulatory approvals based on limited clinical information and the consequent reluctance of some payers to provide these "conditional" therapies to patients in need.

All of these issues, and others, came to the public surface dramatically in the past month after FDA's internally controversial and externally unexpected approval of a new therapy for Duchenne's muscular dystrophy. These are matters of fundamental importance where legitimate experts honestly disagree. They also transcend the world of rare diseases and resonate in a health product ecosystem that faces considerable instability and disruption. There are lessons to be learned; our Special Section (curated expertly by Dr. Vinciane Pirard of Sanofi) illuminates them and helps us all think.

FDA's Dr. Janet Woodcock and Dr. Theresa Mullin recently granted Global Forum an exclusive interview on the reauthorization of PDUFA; we feature it as an audio podcast simultaneously with the publication of this issue. In the interview, their insights on rare diseases, the voice of the patient, evidence generation and innovative trial designs surfaced readily and poignantly.

Two days before the interview, FDA and EMA had announced a new "cluster" on rare diseases.

LET'S START A CONVERSATION!
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Too Rare for Development?

Dr. Vinciane Pirard

For patients suffering from a rare disease, the disease is still too often an isolating experience. Overall knowledge on the disease can be scarce and the quest for a diagnosis and treatment can be long and harrowing. A majority of these patients are young adults or children. Most diseases are congenital or have a genetic origin; some are cancers or have an autoimmune or infectious cause. These are complex, severe and heterogeneous diseases, and each requires highly specialized expertise and care. A few arbitrarily chosen examples of such diseases are: Spina bifida, fragile X syndrome, Guillain-Barré syndrome, multiple myeloma, pancreatic cancer, cystic fibrosis, Duchenne muscular dystrophy and lysosomal storage disorders (e.g., Pompe disease or mucopolysaccharidosis).

Patients are few and scattered across populations. As a therapeutic area, rare disease is a collection of clinical and biological exceptions which makes scientific generalizations that more difficult. But this does not mean that relevant evidence cannot be generated using the right methods. For a very rare disease like mucopolysaccharidosis type II, you will find one affected patient for every 13,000 diabetes patients. These small to very small patient populations bring a special set of challenges to drug developers and public health decision makers. Gathering knowledge and information on these diseases is a major one. Databases, when they exist, are fragmented. Record keeping within health care systems is poor because coding systems such as ICD 10 largely ignore these diseases.

Collectively, however, rare diseases are an important challenge for society: Estimates suggest that 6-8% of the population might be affected by one of 6000 to 7000 rare diseases, a total estimate of 350 million people affected worldwide. Only 5% of rare diseases have a registered treatment. Some can be prevented, and we can decrease the adverse impact of symptoms for others. The need for therapeutic options remains very high but not all diseases will require drug treatments: Some will not be amenable to treatment, some might be treatable with existing molecules, and other diseases are not yet "ready" because the critical body of knowledge isn't mature enough to enable identification of a treatment target or initiation of a development program.

The definition of rare diseases is an arbitrary cut off point that creates a space for policy interventions to address a variety of situations, including stimulating the development of orphan medicinal products to treat these conditions. Historically, individual rare diseases failed to attract interest of researchers, medical specialists, drug developers and policy makers. The biologic revolution, and the growing understanding and deciphering of underlying biologic mechanism, have allowed more innovative treatments to be developed. The 1983 Orphan Drug Act in the US, the 1993 orphan drug legislation in Japan, and the orphan medicinal product legislation of 2000 in Europe, have combined to create economic conditions in which to apply the growing body of knowledge to rare diseases so that every patient has an equitable chance to see treatments developed for their condition regardless of the frequency of their disease. These legislative efforts have been very effective in stimulating collaboration between biopharmaceutical research companies, academic researchers, patient groups and others, to apply the growing understanding of the causes of rare diseases to speed the development of treatments for patients.

It is important to realize there is no universal definition of rare diseases: A recent ISPOR (International Society for Pharmacoeconomics & Outcomes Research) review identified 296 definitions spread across 1109 organizations. The difference between these definitions, and legislation, can confuse analysis of the impact of remediation measures.

At this writing, 578 distinct marketing authorizations with orphan status have been granted in the US. There are 122 in Europe, 29 of which have been withdrawn or expired. Translation of rare disease research into product development and health care innovation is happening across an increasingly large number of diseases. A recent study on the orphan medicinal product designation pipeline in Europe showed that the most common therapeutic area is indeed oncology (36% of the total), followed by neurology and haematology with some clusters observed across diseases like Duchenne muscular dystrophy, haemophilia or cystic fibrosis. Almost half of these designations are for diseases that have no other treatment available at the time of designation.

As of September 2016, for the 598 different diseases with a designated orphan medical product (OMP), 398 (67%) had only one OMP designation, which indicates that development efforts are addressing areas of unmet need. OMPs are disproportionately developed by small companies – approximately 85% of the orphan designations applications originate from small- and medium-sized enterprises (SMEs). These statistics support the fact that the orphan drug framework increasingly enables investors to support funding projects that advance science and meet patient needs even if the total patient population is small.

Eventually, as pioneering efforts are bearing their fruits and stimulate further development for rare disease treatments, the debate will shift to conditions for patients to access these therapies.

One of the main challenges of rare diseases is the persistent uncertainty in the evidence resulting from the limited information on the natural history of the disease and small patient numbers in clinical trials. The following articles will present thinking and initiatives to address these limitations.

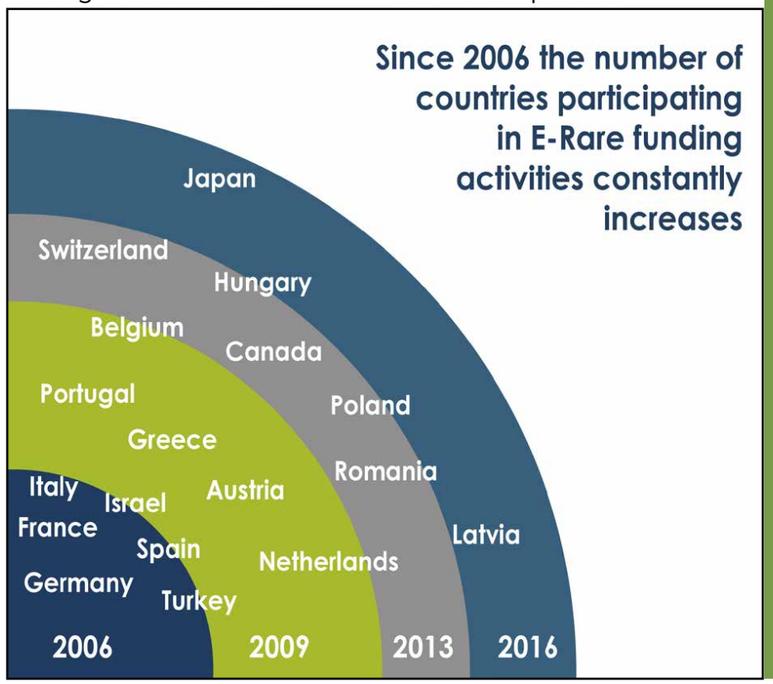
About the Author

Dr. Vinciane Pirard *is the co-chair of the European industry EFPIA-EuropaBio joint task force on rare diseases and orphan medicinal products. She is a member of the EU Commission Expert Group on rare diseases and part of the Sanofi –Genzyme public affairs European team. Dr. Pirard has 25 years of experience, mostly in medical affairs, in the pharmaceutical industry.*

E-Rare Project Celebrates Ten Years of Collaboration in Rare Disease Research

Daria Julkowska, PhD

E-Rare, the **ERA-Net for Research Programmes on Rare Diseases**, was established in 2006 and has since been co-funded by the European Commission. Only a few European countries fund research on rare diseases through specific dedicated programs. Therefore, the funding of transnational collaborative research is the most effective joint activity to enhance the cooperation between scientists working on the unmet medical needs of patients with rare diseases in Europe and beyond, both reducing fragmentation of research in this field and increasing research access to rare disease patients.



The E-Rare consortium was built to link responsible funding organizations and ministries that combine the scarce resources for rare diseases research and thus enable the participation of many researchers to transnational projects via Joint Transnational Calls (JTCs).

At the start of E-Rare-1 in 2006 the consortium consisted of eight countries. In 2016, E-Rare-3 is a network of 26 partners – public bodies, ministries and research funding organizations – from 18 countries (see figure 1 and related table).

MEMBER STATES
FWF & FFG, Austria
FNRS & FWO Belgium
ANR, France
BMBF, DLR & DFG, Germany
GSRT, Greece
NKFIH, Hungary
ISS, IT MoH & RER-ASSR, Italy
VIAA, Latvia
NCBR, Poland
FCT, Portugal
UEFISCDI, Romania
ISCIII, Spain
ZonMw, The Netherlands

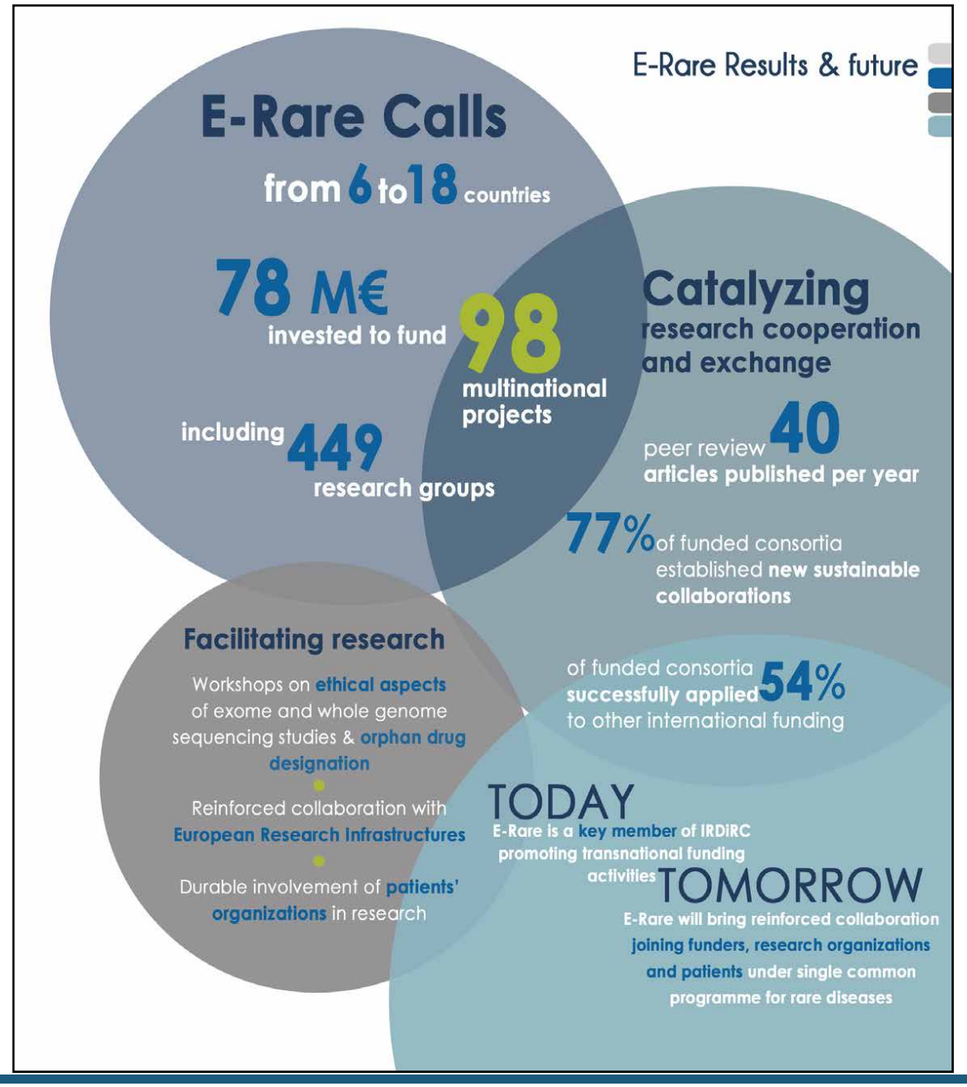
THREE ASSOCIATE STATES
SNSF, Switzerland
CSO/MOH, Israel
TUBITAK, Turkey

OTHER
CIHR, GC & FRQS, Canada
TRI-FBRI, Japan

In addition, E-Rare is a member of the **International Rare Diseases Research Consortium** which aims to achieve two main objectives by the year 2020: To deliver 200 new therapies for rare diseases, and to deliver the means to diagnose most rare diseases via the release of guidelines and recommendations to the rare diseases research communities.

FUNDING ACTIVITIES

In E-Rare's seven JTCs between 2007– 2015, 1021 projects were submitted; 98 projects were funded with a total budget of 78 M€, with 449 research groups involved (see figure 2). Projects funded through E-Rare calls cover a wide range of medical areas, and their outcomes have a clear impact on patients' lives. New causative disease genes were discovered that have a major impact on diagnosis and potential treatment. Better understanding of the natural history of disease through registries and the harmonisation through guidelines will improve treatment of patients. Creation



of animal and cellular models lays the basis for future research into diseases mechanisms and therapeutic options. E-Rare funding opportunities are open every year; in addition to JTC 2016, two other JTCs (JTC 2017 and 2018) are already planned. In addition to funding and monitoring the transnational research projects with measurable indicators, E-Rare also identifies rare diseases research needs to implement specific funding opportunities based upon IRDiRC recommendations since 2012. Three calls have specifically focused on rare diseases research needs: The JTC 2012 call was dedicated to young researchers and clinicians proposing projects on rare diseases; JTC 2014 focused on innovative therapeutic approaches; and JTC 2016 spotlights clinical trials for new therapeutic uses of already existing molecules (repurposing) in rare diseases. Although E-Rare is not principally dedicated to support patients care systems, it aims at contributing to the strengthening of collaboration between research and health services. The JTC 2016 call is a precise example of how E-Rare can influence and strengthen the collaboration between national Ministries of Research and of Health to foster use of repurposed drugs as new therapies with clear benefit to rare disease patients.

FACILITATING RESEARCH & PROMOTING TOOLS

Rare disease research may also benefit from several of the European research infrastructures and other initiatives developed in the past few years. These infrastructures aim at facilitating rare disease researchers' access to resources and knowledge, to contribute to data sharing and avoid duplication of efforts. To enhance its contribution to excellent and sustainable research results, E-Rare established collaborations with a number of these infrastructures (BBMRI-ERIC, EATRIS, ECRIN, Elixir, EU-Open Screen, Infrafrontier), and also with the European Medicine Agency (EMA), to customize their services to meet the unique demands of rare disease researchers. **E-Rare has developed a dedicated portal** to provide information about these services and to link scientists with infrastructures. The E-Rare consortium further promotes use of European infrastructures within its calls for projects.

FOCUS ON COLLABORATION WITH PATIENTS' ORGANIZATIONS

In the last ten years, E-Rare has created a sustainable network of rare disease research funders and collaborators. Since its inception, EURORDIS has been a strategic E-Rare partner but since 2014 has also actively contributed to developing new models of funding and of the implications of involving patients' organisations (POs) in research. A JTC 2016 pilot has already allowed POs to contribute to the evaluation and co-funding of scientific projects. The goal of this process is to establish durable and even-handed partnership between patients, their organizations, funders and researchers.

THE FUTURE OF E-RARE

Since 2006, E-Rare has been a crucial instrument to enhance collaboration between EU Member States in the field of rare diseases research. This effort must be pursued and deployed further to foster a greater level of coordination and integration of the many initiatives already established in Europe, because better research is where better patient health outcomes start.

About the Author

Daria Julkowska, PhD, *is a Scientific Coordinator at ANR, France. She has been involved in E-Rare since 2010, first as project manager and since 2012 as program coordinator. She has developed and put into action a set of collaborations facilitating rare diseases research, including partnerships with European research infrastructures and patients' organizations, to whom she provides her extensive knowledge and understanding of European funding schemes and programmes.*

Conventional Health Economic Evaluation Fails to Capture Social Value of Interventions for Rare and Ultra-Rare Disorders

Prof. Michael Schlander

Orphan drug legislation provided for a broad range of incentives for research and development (R&D) into interventions for the prevention and treatment of rare and ultra-rare disorders. These measures have contributed to a stream of new medications, some of which rank among "the most expensive drugs in the world." In times of economic austerity, health care policy makers need to address whether these interventions offer "value for money." Decision makers struggle with the absence of accepted validated tools how to determine – and how to quantify – the social value of such interventions.

An international group of experts in clinical pharmacology, evidence-based medicine, medical ethics, health economics, and health technology assessment (HTA), analyzed the limitations of the current evaluation paradigm and identified promising alternatives. To date, the group has met five times.

The group reached a consensus that the complexities of R&D of new treatments for ultra-rare disorders may require conditional approval and reimbursement policies, but explicitly shared the view that this flexibility should not be used as an excuse for settling for surrogate endpoint improvement only. Demonstration of clinical effectiveness was considered feasible even in the context of ultra-rare disorders and should be expected within reasonable timeframes, in essence adhering to well-established principles of evidence-based medicine (EBM).

In striking contrast, the conventional logic of cost effectiveness (as advocated by many health economists and used by a number of official agencies in charge of HTAs) does not adequately capture prevailing social norms and preferences regarding health care resource allocation. This is due to its narrow focus on efficiency as defined by incremental cost per quality-adjusted year (QALY), which in effect reduces the problem to three variables – (incremental) costs, life years, and health state utilities – which are combined by a simple algorithm. However, the fundamental assumption underlying the conventional approach, i.e., the presumably increasing social desirability of services associated with decreasing incremental cost effectiveness ratios (ICERs), must be considered as "descriptively flawed."

This creates a serious mismatch between reimbursement policies based on the logic of cost effectiveness (including benchmarks for cost per QALY ICERs) on the one hand, and international policies designed to encourage research and development into rare and ultra-rare disorders and their effective treatment on the other. Clearly, there is a need for a more coherent value framework reflecting all attributes of health technologies deemed

relevant by the public, while at the same time remaining consistent with prior normative commitments as entailed by institutional and legal traditions.

An increasingly large body of empirical research has revealed a broad range of relevant social preferences, which include but are not limited to: Priority for care for the worst off (related to initial health state); for those with more urgent conditions (the so-called "rule of rescue"); a relatively lower priority based upon capacity to benefit; and a dislike against "all or nothing" resource allocation decisions that might disenfranchise certain groups of patients from any chance to access effective care. Furthermore, some studies observed a public preference for allocating parts of a limited budget to services that are effective but not "cost effective," whereas empirical research into the potential role of prevalence (or "rarity") has yielded inconclusive results to date.

For both normative and empirical reasons, conventional health economic approaches (resting on individual willingness-to-pay or cost per quality-adjusted life year [QALY] gained) are not up to the task to capture the full social value of interventions for rare and ultra-rare disorders. Besides multi-criteria decision analysis (MCDA), a particularly promising candidate for a postconventional evaluation paradigm has emerged with social cost value analysis using, for example, the relative social willingness-to-pay or person trade-off instruments for direct social value measurement.

If a social value perspective (instead of a focus on individual utility) was adopted in a consistent manner, this would create implications for the definition of social opportunity cost (or value foregone). Social value being driven by the existence of a health care program (for example, the value people might attach to living in a society that does not abandon certain groups of patients unfortunate enough to suffer from a high cost illness) would imply defining opportunity cost by its budgetary impact. This would obviously shift the focus from cost per patient to cost on the program level, which indeed coincides with the perspective of many real-world decision makers.

References available upon request.

About the Author

Michael Schlander *is founding chairman of the not-for-profit "Institute for Innovation & Valuation in Health Care" (InnoValHC) in Wiesbaden, Germany (as of 2005). He is a health economist at the University of Heidelberg (Mannheim Institute of Public Health, since 2007) and a professor of health care and innovation management at the University of Applied Sciences in Ludwigshafen (since 2002). He is member of scientific associations including the International Health Economics Association (iHEA) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); in 2008, he was a co-founder of the German Society for Health Economics (Deutsche Gesellschaft für Gesundheitsökonomie, DGGÖ). He further acted as scientific program chair for the 15th Annual European Congress of ISPOR.*

FEW PATIENTS BUT STRONG EVIDENCE

Simon Day, PhD

The challenges in researching therapies in rare diseases are well recognized, including the exceptionally low disease prevalence, challenges in identifying or finding patients (let alone adequate numbers of patients), small and particularly very often heterogeneous patient populations, and limited knowledge of natural history.

In response, the International Rare Diseases Research Consortium (IRDiRC) Therapy Scientific Committee recommends:

- Encouraging, supporting and establishing early and continuous dialogue on clinical development strategies and wide evidence generation (e.g., natural history, registry, clinical trial design, clinical endpoints, surrogate endpoints, patient-centered outcomes, regulatory strategy, medical practice, public health strategy) with all relevant stakeholders such as patient representatives, medical experts, researchers, scientific societies, regulators, health technology assessors, payers and sponsors when appropriate. This could be done through dedicated workshops – safe harbours where knowledge could be shared in a non-competitive manner.
- Encouraging, supporting and developing small population clinical trials (e.g., exploring the application of innovative methods). This is an essential step to gather more relevant data at the time of benefit-risk assessment.

In May 2016, to contribute solutions to these recommendations, the IRDiRC Executive Committee convened a Task Force that brought together 35 experts from Europe, the US and Japan. While the Task Force had a strong base of statistical expertise, patients, physicians, regulators, industry members, scientists, and academics all contributed substantially to the group's recommendations.

Six specific topics were identified and discussed in subgroups. Each deserves substantive thought and ongoing research, but the constraints of the workshop meant that each was considered for only about two hours. The following summarises some of the key issues discussed.

KEY ISSUES FOR CLINICAL DEVELOPMENT/TRIALS

- **Different study methods/ designs and different types of conditions:** Randomised clinical trials, with strong, clinically relevant endpoints, and long follow up should be used whenever feasible. However, this is not always possible. To assist choosing a suitable trial design, the following points were considered: cross-over designs; group-sequential designs; inferentially seamless adaptive designs; do not dichotomise continuous endpoints in the primary analysis; minimize censoring in survival trials; and in all studies collecting longitudinal data, let patients stay in trials for as long as possible to maximise information.

- **Adequate safety data:** Safety is an essential component of the benefit-risk profile. The adequacy of the safety database will depend on multiple factors, including the nature and severity of adverse events associated with the product during clinical development, the magnitude of the benefit associated with the product in the studies that provide the primary evidence of effectiveness, and the patients' tolerance for risk. In small studies, clinical trial data alone typically do not give sufficient safety data. Therefore, it is important to combine several data sources (trials, registries, postmarketing data, etc.) to create a fuller safety profile.

- **Multi-arm and platform designs:** Platform trials compare several treatments in several treatment arms, testing each treatment for similar (although not necessarily identical) indications with all arms sharing a common control. The different treatments and trial arms may or may not start at the same time, and treatment arms may be added or dropped as the trial progresses. This trial design may be used in a proof-of-concept phase 2 or definitive phase 3 trial. Such multi-arm trials should be considered by trial funders and patient organisations as an opportunity for rare disease studies. Expertise centres, such as the European Reference Network for rare diseases, should try to channel patient flow towards this trial design, if possible. Funders should be encouraged to fund platform trials via international networks to trial multiple treatments more efficiently.

- **Decision analytic approaches and rational approaches to adjusting levels of evidence:** If sufficient knowledge is available about a treatment, how are the best decisions made and which standards of evidence are required to make them? In this topic, three main questions were discussed.

  1. "If we know enough about a treatment, how do we decide if it is valuable?"
  2. "What standards of evidence do we require?" It is important to realize that the same standard of evidence may not be valid in every disease (especially when the number of patients who may benefit from the treatment is small).
  3. "What technical issues are there regarding decision analytic approaches?" A particular issue is methods for elicitation of informative Bayesian prior distributions.

- **Extrapolation problems and opportunities:** Extrapolation is extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, condition or medicinal product. Data to support extrapolation of efficacy may come from many sources, including pharmacokinetic/pharmacodynamic (PK/PD) models but also registries, off-label data, or electronic health records. The quantity and quality of data to be used for extrapolation, as well as the time for extrapolation (early phase trials, late phase trials), is still decided on a case-by-case basis.

- **Patients' engagement in study design:** The patients' voice is essential in the set-up of clinical trials but at present there is no clear process, nor consensus, on the best way to incorporate this voice. Consultation with patients experienced in clinical trials is advised – and the earlier, the better. The pharmaceutical industry is still relatively inexperienced on how to incorporate patients' opinions into the trial process, and should look to guidance from regulatory and patient organizations.

CONCLUSIONS

When setting up a clinical trial for a rare disease, a systematic look at alternative design options, beyond the traditional randomized controlled trial, is advised. Not every rare disease trial is as challenging as others, but if a randomized control design is not feasible, consider other trial options. Better use of scientific advice from regulators regarding trials in rare diseases should be promoted. Regulators are often very accepting and supportive of novel designs, provided they are well thought through and justified, and welcome discussions and questions on this topic.

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About the Author

Dr. Simon Day *has spent 30 years working in the pharmaceutical industry, including five years at the UK and European regulatory agencies. He now serves as a worldwide statistical and regulatory consultant to pharmaceutical companies as Director, Clinical Trials Consulting & Training Limited, and as Regulatory Advisor Board Member for NDA Advisory Services Ltd. He is Chair, IRDiRC Task Force on Small Population Clinical Trials, and is particularly well-known for his work in the area of developing treatments for rare diseases.*

Australia/New Zealand Regional Report

TGA Head: Australia Moves to Improve Medicines Labeling & Nomenclature

Richard Day, AM, MD, FRACP
DIA Fellow and
DIA *Global Forum* Australia / New Zealand Regional Editor


Dr. John Skerritt

Dr. John Skerritt is Deputy Secretary of the Australian Department of Health and is responsible for the Therapeutic Goods Administration (TGA). He was pleased to answer questions about new medicines labels and changes in medicines nomenclature for this Regional Report.

RD: Could you highlight the improvements in medicines labels?

JS: Important information will be easier to find. Active ingredients will be in larger text size and in a consistent location on the medicine label. For OTC medicines, critical health information will be displayed in a consistent order and easily recognizable. For prescription medicines, there is now more blank space on a label so the pharmacist can attach a dispensing label without covering up other important information.

RD: Are you happy with the process that led to the changes?

JS: Yes. There was a significant amount of stakeholder consultation including with industry, consumer groups, health professionals and the community, before the changes were made. This consultation process and development of the changes took several years. Overall, the response from stakeholders has been very positive.

RD: Do you foresee any challenges?

JS: During the four-year transition period, consumers will see both "old and "new" labels. Although this may cause some initial confusion to consumers, it was necessary to ensure industry had enough time to update their labels and for pharmacists to sell their existing stock.

RD: And what about the medicines nomenclature changes? Why were these introduced?

JS: In different countries, different names may be used to describe the same medicinal ingredient and some of the names in Australia had become obsolete. This can be confusing for Australian consumers and health care professionals who travel internationally, as well as for health care professionals who have trained overseas or for people trying to access medicine information online.

RD: How were the new names sourced?

JS: Where possible, the TGA adopted the global standard for medicine ingredient names, namely the International Nonproprietary Names (INNs). Where an INN doesn't exist, the TGA used pharmacopoeial references as sources of the new ingredient names.

RD: Will there be risks of medication errors and how will these be addressed?

JS: The TGA has been working closely with industry, health care professional, and consumer groups, to develop communication and education materials to minimize the risks of medication errors. **A series of posters and leaflets to help raise awareness of the changes are available on the TGA website.**

Where an ingredient name has significantly changed, the medicine label and product information must also use both the old and new ingredient name for four years. This will help consumers and health care professionals become familiar with the new name.

Canada Regional Report

Informing, Protecting & Welcoming Colleagues to Ottawa

Kimby Barton
DIA *Global Forum*
Canada Regional Co-Editor

As part of its continued commitment to enhance openness and transparency, Health Canada began posting Canadian clinical trial related information on the **ClinRegs website** this past September. This website, hosted by the US National Institutes of Health (NIH), provides country-specific clinical trial information and allows users to explore policies and regulations within a country and compare requirements across countries. It currently contains clinical trial information from 16 countries. Health Canada has worked with the NIH writers to develop materials for the site, including references to the Canadian Food and Drug Regulations, and Health Canada and International Conference on Harmonisation (ICH) guidance documents. The focus is on seven different topics of interest: Regulatory Authority, Ethics Committee, Clinical Trial Lifecycle, Sponsorship, Investigational Products, Informed Consent and Specimens. For readers interested in knowing something about Canadian clinical trial guidance and regulations, we invite you to **visit this website.**

OPIOID STATE OF EMERGENCY IN BRITISH COLUMBIA

From a patient safety perspective, Canada continues to grapple with an overwhelming number of opioid deaths, particularly in British Columbia. The Province has declared a state of emergency, and has reached out to the Federal Government for assistance in managing the crisis. In January 2016, Health Canada changed the status of naloxone from prescription to non-prescription to increase accessibility, and more recently, the Government has repealed a law that prevented patients with chronic recurrent opioid dependence from accessing heroin as a treatment through Health Canada's special access programme. Health Canada has also released an action plan on opioid misuse that focuses on providing better information on the risks of opioids, supporting better prescribing practices, reducing easy access to unnecessary opioids, supporting better treatment options for patients, and improving data collection on opioid misuse and abuse.

IRF & DIA: WELCOME TO OTTAWA!

In October, DIA will welcome our colleagues to the **DIA Annual Canadian Meeting 2016**, titled, "*Innovation to Support Collaboration, Engagement, and Openness Across the Canadian Health Care Landscape*." This year, for the first time, Health Canada has aligned its International Regulatory Forum (IRF) with the DIA event calendar so that foreign regulators who come to Ottawa for the IRF can also attend the *DIA Annual Canadian Meeting.*

The IRF was developed to provide comprehensive information about Health Canada's regulatory processes to international regulatory counterparts, and its meeting program will addresses the Canadian regulation of health products throughout the pre- and post-market product life cycle. The DIA Meeting will open with two short courses, one on the **implementation of the new plain language labelling guidance** and another on **innovation in prescription to non-prescription switches**.

Also for the first time, attendees are invited to join colleagues on the evening of the meeting's first day to create packets for the waiting room for the **Children's Hospital of Eastern Ontario (CHEO)**. Please join your colleagues at this fantastic event!

Europe Regional Report

In the Meantime... Affordability & Access

John Lisman
DIA *Global Forum*
Europe Regional Editor

Our last two regional reports have addressed the EU – UK relationship. We will leave this topic to rest, because it seems that we will not know exactly what will happen in the coming months and years. In the meantime, other interesting issues in Europe remain, especially initiatives undertaken to address access to medicines for all and early access to innovative medicines.

AFFORDABLE MEDICINES

The Dutch EU presidency (in the first half of 2016) organized a large meeting about, among other things, pricing and reimbursement of medicinal products, rewards for investments in innovation, and the importance of affordability of medicines. This led to **"Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States."** Interestingly, while emphasising the EU's limited remit to issues relating to free movement of goods, services, persons and capital, Health Ministers expect EU level actions as well as collaboration between (clusters of) Member States above the Member State level. Note 16 of this document mentions one reason: "Increasing number of examples of market failure in a number of Member States, where patients access to effective and affordable essential medicines is endangered by very high and unsustainable price levels, market withdrawal of products that are out-of-patent, or when new products are not introduced to national markets for business economic strategies and that individual governments have sometimes limited influence in such circumstance."

It seems that one of the problems in the EU is to balance the principle of a single market with the principle of solidarity, which leads to the desire to treat all EU citizens at the same level. The problem with this is that huge GDP differences exist between north and south, and between east and west, which leads to a completely different meaning of "affordable" depending on where you are. This discussion is not only relevant to the EU and politicians in its Member States, but even more important for European health care professionals and their patients. Last but not least, squaring this circle requires pharmaceutical industry input; after all, if patients cannot afford to use their products, the companies manufacturing and marketing them cannot recoup their investments.

MAPPS: TIMELY ACCESS TO INNOVATION

To develop an innovative medicinal product takes a long time and getting the product approved creates even more delay. But patients with life threatening diseases do not have time to wait. The Medicines Adaptive Pathways to Patients (MAPPS) project aims at early access to medicines via Adaptive Pathways, which uses alternatives to the normal marketing authorisation procedures. The idea is to approve early use of the medicinal product in a narrow therapeutic area, then allow broader use incrementally. Competent authorities will approve early use in return for agreement on strict product monitoring and postmarketing commitments. Adaptive pathways is not a new route of marketing authorization. It makes use of existing approval tools, in particular the conditional marketing authorization available in the EU since 2006. It also builds on experience gained with strengthened postmarketing monitoring tools introduced by the 2012 Pharmacovigilance Legislation. The EMA conducted an adaptive licensing pilot project between March 2014 and July 2016, and reported on its promising outcomes in July 2016. The pilot also helped to identify a number of aspects for further reflection: These include the need for increased patient involvement in the selection of candidates for adaptive pathways, the definition of methodologically-sound strategies for real-world evidence collection to support both the efficacy and effectiveness assessment and the potential involvement of payers – Member States' organizations responsible for decision on pricing and reimbursement – to provide input on pricing strategies. The MAPPS project is part of the Innovative Medicines Initiative (IMI), the world's largest public private partnerships in life sciences with a €3.3 billion budget for the period 2014-2024.

ACCESS TO AUTHORIZED MEDICINAL PRODUCTS

In the EU, as in other parts of the world, medicinal products are used off-label to a large extent. This means that many patients are treated with medicines that have not been tested or evaluated for the purpose they are used for in medical practice. This topic is being addressed by the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), formed to provide a forum for the Commission and Member States to discuss off-label use and what to do about it on the basis of a **report by the Belgian Healthcare Knowledge Centre.** One of the most attractive strategies for solving the issue of off-label use is to turn off-label into on-label use by authorizing the off-label use, often referred to as drug repurposing or rediscovery. One of the main problems in this strategy is the lack of incentive for the marketing authorization holder to invest in clinical development after the patent and supplementary protection certificate have already expired.

IN CONCLUSION

Many exciting developments, all focusing on better and earlier access to medicinal products that have been assessed by competent authorities, can lead us to hope that all these initiatives may lead to better treatment options for our patients.

References available upon request.

Europe Regional Report

EU-US Collaboration to Boost Medicine Development for Rare Diseases

NEW WORKING GROUP WILL SHARE INFORMATION AND BEST PRACTICES

The European Medicines Agency (EMA) and the US Food & Drug Administration (FDA) have set up a new **"cluster"** on rare diseases to share experiences and best practices on each other's regulatory approach to the development of medicines for these diseases.

While rare diseases are estimated to affect 30 million people in the EU and approximately the same number in the US, each disease individually concerns a limited number of patients. Therefore, global collaboration in this area is particularly important to ensure that the limited number of studies that can be conducted, due to the small populations, can benefit all patients regardless of where they live.

The agencies will exchange information on various aspects of the development and scientific evaluation of medicines for rare diseases. These include topics such as:

- Design of clinical trials in small populations and the use of statistical analysis methods
- Selection and validation of trial endpoints, i.e., target outcomes of a trial
- Preclinical evidence to support development programs
- Design of postmarketing studies, in particular in the context of early access mechanisms such as EMA's **conditional marketing authorisation** and FDA's accelerated approval
- Risk management strategies for long-term safety issues with medicines for rare diseases.

The cluster will provide a forum for confidential exchange of draft documents, policies under development, and more detailed information supporting the scientific basis for decision making on medicine development.

The existing EMA/FDA "cluster on orphan medicinal products" will continue to focus on information sharing and collaboration on orphan designation and exclusivity, the agencies' mechanisms to encourage the development of medicines for rare diseases.

The first meeting of the rare diseases cluster took place by teleconference on 23 September 2016. The cluster will initially meet once a month via teleconference and will be chaired jointly by FDA and EMA.

The creation of this cluster is the latest step in EMA's and FDA's wider objective to expand and reinforce international collaboration.

The clusters established by EMA and FDA focus on areas where the parties involved could benefit from an intensified exchange of information and strengthened collaboration. The existing EMA/FDA clusters discuss issues related to patient engagement, biosimilars, orphan medicines, medicines to treat cancer, medicines for children, and pharmacovigilance, among other topics.

The information exchange is covered by the confidentiality arrangements between the two regulators.

Japan Regional Report

When Should Foreign Sponsors Appoint Their ICR in Japan?

Shogo Nakamori

The proportion of multinational clinical trials that include Japan has grown from 7.4% in 2007 to 28.1% in 2013, and the Japan market remains very attractive because it is the second largest single-country market (after the US).

During the last decade, the number of foreign sponsors who have no legal entity in Japan but plan to conduct clinical trials in Japan for market authorization has grown rapidly. It is essential for these sponsors to address the requirement of Clinical Trial In-Country Representative (ICR) in order to comply with Japan Good Clinical Practice (J-GCP) regulations.

J-GCP Article 15 stipulates that a foreign sponsor who has no legal entity in Japan but wants to conduct clinical trials in Japan must appoint an ICR to oversee the trial. This ICR assumes no legal responsibility, unlike local sponsorships in other countries; Japan MHLW regulations only specify that the ICR shall endeavor to appropriately manage clinical trial operations. The foreign sponsor is subject to corrective orders and/or disciplinary actions from the Authorities if anything goes wrong in the study, regardless of who actually conducted it. This is quite different from regulations governing INDs (e.g., 21 CFR 312.52), which transfer regulatory obligations from the sponsor to an agent of the sponsor in the US.

So, when should foreign sponsors appoint their ICR? The earlier you appoint them, the better your chances of a successful trial. Foreign sponsors may consider organizing a consultation meeting with PMDA before even starting their trial and include the ICR in the meeting. Even though foreign sponsors can defer appointing their ICR until after their PMDA trial consultation, it is highly recommended to appoint this ICR prior to this meeting. By engaging a person or entity capable of assuming the ICR roles and responsibilities prior to the PMDA meeting, a foreign sponsor can develop a more comprehensive clinical strategy leading to JNDA submission.

Foreign sponsors often incorrectly identify the start of their obligatory safety reporting period. These obligations starts from the day their CTN (Clinical Trial Notification) is submitted and they last to the day of product approval or when drug development is terminated. Sponsors must also prepare their safety management plan in time to start safety reporting upon CTN submission.

PMDA clearly states that any entity appointed as an ICR must not only provide the services contracted with the sponsor but they must also ensure that foreign sponsors acknowledge and comply with Japan regulations.

About the Author

Shogo Nakamori *serves as Corporate VP, CRS, Asia-Pacific & GM Japan Country Operation, PAREXEL International.*

Japan Regional Report

THINK: Are Your Risk Minimization Activities Really Effective for Patients and HCPs? *DIA Japan 3rd Risk Management Workshop*

Rei Maeda
Program Chair

Junichi Nishino
DIA *Global Forum*
Japan Regional Editor

Safety measures and related efforts have been in place in Japan for more than twenty years. These activities were at first relatively independent from each other and reactive, even after agreement on ICH E2E (pharmacovigilance planning) was reached in 2005. In April 2012, a Risk Management Plan (RMP) guidance was developed in Japan based on E2E; it encourages integrating three safety components – Safety Specifications (SS), Pharmacovigilance Plan (PvP) and Risk Minimization Plan (RMiP) – into one RMP to more proactively prevent and mitigate therapeutic risks. It became effective in April 2013.

The *DIA Japan 1st Risk Management Workshop* that took place in 2014 mainly focused on establishing the SS scientific rationale. In 2015, the *2nd Risk Management Workshop* focused on building a PvP that leads to the right research questions and answers.

The *2016 DIA Japan 3rd Risk Management Workshop* focused on the RMiP component. Participants at this workshop included more academic/clinical pharmacists than the previous two, which were mainly attended by participants from industry/CROs and PMDA. This provided these key stakeholders with discussion opportunities from developer, reviewer and customer perspectives.

Workshop speakers provided other rich content. Dr. Stewart Geary (CMO, Eisai Co., Ltd.) concisely presented the essence of CIOMS IX, where he is a core member. Each of several smaller breakout groups determined the SS and developed an appropriate RMiP, considering CIOMX IX, for fictional "Product X." Each group then presented the rationale, feasibility and burden of their results. After Ms. Shohko Sekine (Reviewer, Office of Safety II, PMDA) explained PMDA review tips for RMPs in Japan, an interactive Q&A session and panel discussion closed the workshop.

Through the workshop, we learned that;

- It is worthwhile to complete the risk minimization strategy before starting to create documents and tools.
- Importance of "risk-centric" tools was recognized by industry persons, and the difficulty of developing an appropriate tool was also demonstrated.
- It seems that more time is needed to implement approaches to evaluating the effectiveness of risk minimization measures.
- The next challenge is to break away from current excessive formalism and to develop risk-based, effective and efficient risk minimization tools.

Participants from every stakeholder perspective provided feedback:

- "I learned a lot of different opinions about RMP/RMiP from different standpoints within and beyond my group" (industry participant)
- "I realized what industry persons would concentrate on with enthusiasm when they develop RMiP tools, and also that they have less knowledge about real-world situations in daily practice than we assumed" (clinical pharmacist)
- "We understood the importance of considering the feasibility and effectiveness of RMiP from the customer point of view" (PMDA officer).

We are grateful to all program members who provided their expertise to this workshop.

Middle East and Africa Regional Report

NEW REGULATORY BODY FOR SOUTH AFRICA

Vincent Ahonkhai
DIA *Global Forum*
Middle East and
Africa Regional Editor

MCC TRANSITIONS TO SAHPRA

South Africa's **Medicine Control Council (MCC)** is in the final stages of preparing to transition into the South African Health Products Regulatory Authority (SAHPRA). Meanwhile, MCC has recently **implemented its guidelines** on the regulation of medical devices and *in vitro* diagnostics.

PROMISING TB DIAGNOSTICS INITIATIVES

The **Global Laboratory Initiative for Africa (GLI Africa)**, a public-private partnership, recently announced its goal to strengthen TB diagnostics in Africa by developing new approaches based on international standards. GLI Africa convened its maiden workshop in Kampala, Uganda on July 19-21, 2016, attended by more than 100 stakeholders and experts from Africa and other parts of the world. Publication of GLI Africa's new approaches is eagerly awaited by all concerned.

US Regional Report

FDA Proposes New Rule on GLP Quality and Oversight

Ann Meeker-O'Connell
DIA *Global Forum*
US Regional Editor

On August 24, 2016, the US FDA published a proposed rule amending its **Good Laboratory Practice (GLP) regulations for nonclinical laboratory studies**. This proposed rule comes six years after **FDA published an Advanced Notice of Proposed Rulemaking (ANPRM)** notifying stakeholders of its intent to amend these regulations. FDA acknowledged that "nonclinical studies have changed markedly" since GLP regulations were issued in 1978, and through the ANPRM, the Agency sought stakeholder feedback on topics it deemed ripe for revision, including the GLP Quality System, Sponsor Responsibilities, Multisite Studies, and Animal Welfare. The proposed rule incorporates changes in each of these areas (see table).

In describing the proposed rule, FDA focuses on how a GLP Quality System will build quality into study design, conduct and reporting, which the Agency anticipates will result in "more reliable data." FDA states explicitly that, "ensuring data quality and integrity...is one of our critical goals in this Part 58 proposal." In keeping with this goal, the proposed rule includes a new section outlining data quality and integrity requirements. This section defines quality data as "accurate, legible, contemporaneous, original, and attributable" – the well-known **"ALCOA principle"** coined in the 1990s. In addition, the section requires all data collected during a study to be in the final study report to avoid bias from selective data inclusion. Concerns about the potential for bias are also reflected in other new requirements; for example, FDA proposes that testing facility management with executive responsibility review all protocols to ensure, among other things, that "issues with scientific methodology do not ... bias any phase of the study's conduct."

Continuing this quality theme, FDA also proposes modifying existing Quality Assurance Unit (QAU) requirements. Some changes alleviate challenges that have arisen from applying a 1978 rule in an era of electronic recordkeeping. Others, however, emphasize FDA's expectations for QAU oversight. For example, the proposed rule requires the QAU to review the study protocol before study initiation and to provide management with executive responsibility and the study director with periodic reports on compliance status of each study. The Agency also clarifies its own oversight, including its authority to inspect any person conducting a phase of a study with an FDA-regulated product and to inspect all QAU records when necessary to ensure compliance with Part 58.

FDA is seeking comments by November 22, 2016, on its proposed changes to Part 58. The timing of the final rule depends on the nature and volume of comments that FDA receives, but the Agency, much like its stakeholders, is already looking ahead to implementation. FDA proposes that any final rule would be effective one year after its publication date.

References available upon request.

TABLE 1: KEY TOPICS AND PROPOSED CHANGES TO 21 CFR PART 58

GLP Quality System	The proposal defines a flexible framework for a GLP Quality System for testing facilities and sites. FDA focuses attention on "management with executive responsibility (MWER)" in revised §58.31. FDA charges MWER with, among other things, establishing and maintaining a quality policy and specific SOPs; conducting periodic management review; and assessing the effectiveness of the QAU.
Sponsor Responsibilities	A new section [proposed §58.5] expands sponsor obligations related to protocol content and approval, sponsor contracting, transfer of responsibilities, communication, and submissions to FDA. Ultimately, the sponsor must include a compliance statement in any application or submission to FDA affirming compliance with part 58 or succinctly describing the reason for noncompliance [proposed §58.5(k)].
Multisite Studies	The proposed rule includes new definitions (e.g., test site), roles (e.g., principal investigator), and requirements to account for the growth of multisite studies in which different study phases may be carried out by different parties. FDA highlights that many of these changes are consistent with the Organization for Economic Co-operation and Development (OECD) consensus document, *The Application of the OECD Principles of GLP to the Organization and Management of Multi-Site Studies.*
Animal Welfare	The preamble notes that "test animal concerns are an essentially part of a GLP quality system," and accordingly, FDA introduces roles (e.g., an attending veterinarian) as well as requirements throughout the proposed rule to ensure appropriate attention to animal welfare. For example: • Sponsors would be required to contract with persons accredited in animal welfare, or to document in an application or submission to FDA why an unaccredited party was used (proposed §58.5). • An animal welfare committee must review and approve the protocol and relevant amendments prior to their implementation (proposed §58.120).

DIA

2016 UPCOMING OFFERINGS OCTOBER-DECEMBER

AMERICAS

OCTOBER 17-18 | WASHINGTON, DC

Risk Management and Safety Communication Strategies

Study current initiatives and new strategies to advance safe drug use through better communication that maximizes patient benefits while minimizing the risks of use.

OCTOBER 17 | SHORT COURSES
OCTOBER 18-19 | MEETING
OTTAWA, ONTARIO, CANADA

DIA Canadian Annual Meeting 2016

Engage with key thought leaders, industry experts, academics, and Health Canada representatives to explore how innovation can drive and support new initiatives, regulatory processes, research, use of real-world data, and much more.
DIAglobal.org/Canada

OCTOBER 24-25 | PHILADELPHIA, PA

Postmarketing Drug Safety and Pharmacovigilance

Explore the fundamentals of clinical drug safety and key postmarketing pharmacovigilance tools, and deepen your understanding of procedures and requirements required to protect patient safety and comply with legal obligations.

OCTOBER 24-27 | PHILADELPHIA, PA

Regulatory Affairs: The IND, NDA, and Postmarketing

Examine FDA regulations and expectations for the content, submission and review of INDs/NDAs, and the importance of regulatory strategy.

OCTOBER 24 | SHORT COURSE
OCTOBER 25-26 | MEETING
WASHINGTON, DC

Combination Products Conference 2016

The increasing importance of combination products – products combining a drug, device, and/or biologic – in innovative medical therapies raises significant regulatory challenges for regulators and industry. *Combination Products 2016: Current, Evolving, and Future Pathways* will examine combination product policy and regulation, and their impact on the life cycle of these products.
DIAglobal.org/Combo16

OCTOBER 26 | SHORT COURSE
OCTOBER 27-28 | CONFERENCE
WASHINGTON, DC

Biosimilars Conference 2016

Discuss biosimilars science, global regulatory pathways, evidence for clinical applications, and education for prescribers and patients, which is critical to successful uptake of these products.
DIAglobal.org/Biosimilars

OCTOBER 31-NOVEMBER 1 | WASHINGTON, DC

Navigating Chemistry, Manufacturing, and Controls Through the Drug Development Process

Equip yourself with the tools you need to write and/or assemble CMC sections of regulatory submissions, prepare for and orchestrate CMC meetings with the FDA, and support regulatory compliance.

DECEMBER 5-6 | WASHINGTON, DC

Advancing the Science of Study Endpoints Conference

Discover global strategies for selecting study endpoints and the impact of study endpoints during analysis of clinical evidence in various drug approval processes. Key stakeholders will address critical questions and potential solutions to challenges associated with determining study endpoints and outcomes.
DIAglobal.org/Endpoints

DECEMBER 7-8 | WASHINGTON, DC

Adaptive Design in Clinical Trials: When and How to Apply

Identify opportunities to apply adaptive design in early- and late-phase development using practical examples that demonstrate how to appropriately design and implement adaptive design trials in compliance with FDA Guidance.

ASIA

CHINA

OCTOBER 24-26 | SUZHOU, CHINA

The 2nd DIA China Drug Discovery Innovation Conference

DIA will join hands with BioBAY—the most influential Science Park for Drug Innovation in China—for the *2nd DIA China Drug Discovery Innovation Conference* in Suzhou. Don't miss the great opportunity to have brain storming sessions with these decision makers and key thought leaders.
eventbank.cn/event/5981

NOVEMBER 7-8 | BEIJING, CHINA
NOVEMBER 10-11 | SHANGHAI, CHINA

FDA/DIA GCP Inspection and Data Integrity Workshop

Good Clinical Practice (GCP) is a compilation of best practices and quality standards to be applied to the overall process of a clinical trial. The FDA China Office will host this two day workshop with specific focus on the US FDA, EMA, and CFDI of CFDA's inspections, data integrity, BE study, and the related topics that affect the quality standards of a clinical trial in Beijing and Shanghai.
eventbank.cn/event/6179

NOVEMBER | BEIJING, CHINA
NOVEMBER 21-23 | SHANGHAI, CHINA

The 6th DIA China Clinical Project Management Workshop

Intermediate to Advanced Level

This is a hands on skills-based course where you will work on your own project(s). The skills gained from this course will enable you to better construct your own RFPs, proposals, SOW, TOAs, Project Plans, Communication Plans, and Close Out Plans.
cn16989.eventdove.com

DECEMBER 16-18 | SHANGHAI, CHINA

2nd DIA China Medical Affairs Advanced Workshop

Building on the success of the recent in-company trainings in several multinational pharmaceutical companies in China, and the tradition of the annual flagship meeting on the same topics in the United States, this three day course is designed to provide medical affairs professionals with the essential skills ranging from medical writing and medical communication, to safety and pharmacovigilance consideration.

DECEMBER 8-9 | SHANGHAI, CHINA

Vendor Selection, Qualification, and Management Workshop

Gain an overview of how to develop expertise for strategic sourcing and negotiation to offer an end-to-end service for customers that will make us a valued partner in the execution of their business objectives, This workshop will focus on vendor selection, qualification, and management for outsourced clinical study as well as center lab testing.
cn16950.eventdove.com

INDIA

NOVEMBER 14-17 | NEW DELHI, INDIA

5th Global Animal Health Conference 2016

Sound governance and alignment to international standards promotes improved animal health that in turn contributes to socio-economic development. Join government representatives, regulators, senior animal health experts, industry, academia, inter-governmental bodies, and international organizations as they exchange views on the importance of good regulatory governance of veterinary medicines.

JAPAN

OCTOBER 27-28 | RYOGOKU, JAPAN

6th Cardiac Safety Workshop in Japan

The *6th Cardiac Safety Workshop* in Japan will provide the latest information on the CiPA testing strategies, while still in development, and their supporting science. Join leading clinical, industry and regulatory experts from all ICH regions to discuss these and related topics at the *6th Cardiac Safety Workshop* in Japan.
DIAglobal.org/CS-JP

NOVEMBER 12-15 | TOKYO
BIG SIGHT ARIAKE, JAPAN

13th DIA Japan Annual Meeting 2016

Breakthrough in Regulatory Science for Patient-Engaged Medical Treatment

The 13th DIA Japan Annual Meeting 2016 will provide the forum where academia, government, and industry discuss these new technologies and breakthroughs for regulatory science research. While the number of stakeholders is increasing due to the global scale of medicine development, we have designed this meeting as an opportunity to consider our highest priority: Patients.
DIAglobal.org/Japan2016

NOVEMBER 13-15 | TOC ARIAKE, JAPAN

ICH/DIA Joint Tokyo Workshop after ICH Japan Meeting

Future ICH activities have the same direction as DIA, which has served as a global forum to increase ICH's global reach. This presents a great opportunity for a joint collaborative ICH/DIA workshop after the ICH Osaka Meeting (November 5-10) and the DIA Japan Annual Meeting (November 13-15), to share with DIA stakeholders the major outcomes, and their implications, from the ICH Osaka Meeting.
DIAglobal.org/ICH-JOINT

EUROPE

OCTOBER 27-28 | DUSSELDORF, GERMANY

Clinical Forum for Operational Excellence

2016 is a key year with notable changes in the clinical landscape with the new Regulation and ICH guideline. The Clinical Forum is unique amongst European conferences in bringing together thought leaders from all core disciplines in clinical research - clinical operations, data management and drug safety – to discuss the implications and discover best practices with professional colleagues, providing an excellent opportunity for networking.
DIAglobal.org/ClinicalForum

NOVEMBER 9-10 | BRUSSELS, BELGIUM

4th European Biosimilars Conference

This two day conference will provide an update on the current status for biosimilars in the EU and internationally with focus on both regulatory and scientific challenges as well as market access and experiences. Patients and physicians approach to use of biosimilars will be part of the conference scope including a discussion on biosimilars adoption into current treatment guidelines in EU. The conference will consist of plenary lectures followed by interactive panel discussions providing you an opportunity to bring forward your own experience and share your thoughts and ideas with the experts.
DIAglobal.org/EuroBiosimilars

NOVEMBER 29-30 | BERLIN, GERMANY

10th Annual European Medical Information and Communications Conference

This is a unique conference organized by medical information professionals for medical information professionals. The speakers share hands-on experience of dealing with current challenges as well as successes. It provides opportunities to showcase success stories or stories to learn by, in the popular *Putting Theory into Practice* session and to explore the impact of new technologies on information delivery and customer interactions. A dedicated poster session will also provide an opportunity to broaden the topics at the conference to other areas.
DIAglobal.org/EuroMedComm

NOVEMBER 29-30 | VIENNA, AUSTRIA

DIA Interactive Hands-on Workshop on the New European Medical Device Regulation: Change Management

This workshop will provide insight to the essential changes of the New Medical Device Regulation, such as the role of notified bodies and requirements in clinical and post-market requirements. Focus on developing skills to apply the New Medical Device Regulation updates to your daily work; you will work through practical application scenarios of the updates with key subject matter experts.
DIAglobal.org/MDR

DECEMBER 6-7 | LONDON, UNITED KINGDOM

Clinical Trial Regulation Conference

The implementation of the Clinical Trial Regulation is getting closer and there are many developments going on at European and Member State level, both in the area of endorsement of the new regulation and development of the Portal and Database. This conference brings together experts from regulatory and industry to discuss and shape best practices to ensure preparedness for the new systems to be established. The conference has a joint day with Disclosure and Data Transparency Conference.

Participants can upgrade to attend both conferences.
DIAglobal.org/ClinicalTrialsWS

DECEMBER 7-8 | LONDON, UNITED KINGDOM

Clinical Trial Disclosure and Data Transparency Conference

The continuing expansion of disclosure requirements in the US and EU leave many sponsors and academia considering disclosure strategy, developing operational measures, and looking for efficient ways to manage dissemination of clinical trial protocol information and results data. The users of clinical trial information is varied which provides both opportunities and challenges for how the information is provided. The conference has a joint day with Clinical Trial Conference.

Participants can upgrade to attend both conferences.
DIAglobal.org/DataDisclosureTransparency

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DIA

DIRECTOR, DIA GREATER CHINA, RETURNS TO "CIRCLE OF FRIENDSHIP"

Carol Zhu, MBA

In February 2016, DIA Greater China welcomed Carol Zhu as Senior Vice President/ Managing Director. She joined DIA from the Bill & Melinda Gates Foundation, where she served as the Senior Program Officer for R&D Programs. Before to her work at the Foundation, she was the founder and CEO of START Shanghai, one of the first phase 1 oncology service companies in China.

Ms. Zhu brings to DIA China twenty years of experience in clinical research, business operations, and project management in the pharmaceutical industry. Her work was key in establishing GSK's R&D Center in Shanghai, where she led the clinical and business operations. She received her BS degree in Pharmaceutical Science from Peking University Health Science Center (Beijing Medical University) and her MBA from Rutgers University (US). In the midst of preparing our ***2nd DIA China Drug Discovery Innovation Conference***, Ms. Zhu spoke to *Global Forum* Deputy Editor Dr. Alberto Grignolo about the progress, and promise, of DIA Greater China.

AG: What most attracted you to DIA as the organization through which you could serve the health care community in China?

CZ: I have been a DIA member and DIA speaker since about ten years ago. I have witnessed the evolving of clinical research in China since 2000. It has been exciting to see the improvement of clinical quality that has created new career development opportunities for young people. DIA has played a critical role to bridge international drug development systems, thoughts, and regulations, and has created a vital network and community via the Advisory Council of China (ACC) to lead various training and meeting activities. I have worked with many of the ACC members and have been friends with some of them as well. Therefore, when I left the Bill & Melinda Gates Foundation to join DIA China as the Senior Vice President and Managing Director in February 2016, I felt that I was back into this circle of friendship.

AG: Do you feel that your work at the Bill & Melinda Gates Foundation helped to prepare you for this opportunity with DIA and if so, how?

CZ: Yes, very important help! I was amazed to see how things work for a good purpose. At the Gates Foundation, I was particularly focused on building partnerships with government agencies such as the Ministry of Science and Technology (MOST); the China Food and Drug Administration (CFDA); and the National Health and Family Planning Commission (NHFPC). This experience had helped me appreciate to the complexity and sensitivity of working approaches, balancing the objectives of both governmental and non-governmental organizations: Respect, understanding and patience are required to achieve the ultimate goal of fostering innovation to improve health and well-being worldwide. I am very glad to see some of my work come to fruition: In June 2016, the CFDA and Gates Foundation signed a Memorandum of Understanding establishing mechanisms that will introduce international high-end talent for drug supervision. It would be a synergistic area for DIA as well.

AG: What do you see as China's unique contributions to global health care?

CZ: The growth of China's pharmaceutical market continues to be strong, with double-digit growth per year; in 2014, it totaled $200.2B (USD), with a compound annual growth rate (CAGR) of 16.5%. The medical device market expanded significantly with a CAGR of 20.8%. R&D funding has grown at 27% CAGR over the past five years, and is estimated to increase to $25-30B (USD) in 2025 (according to McKinsey data). We have seen very vibrant R&D, M&A or investment deals in China during the past year, with a noticeable trend of multinational corporations collaborating with Chinese R&D companies.

Chinese innovative enterprises and companies have shown a new interest in R&D investment in China. eHealth solutions have attracted a lot of venture capital investment to help us address the health care challenges facing the world's largest population and its growing aging problem.

AG: What are the two or three areas in which DIA can have the most immediate – short-term – impact in China's health care community? Further down the horizon, what is your vision for DIA's long-term prospects in China?

CZ: Building the effectiveness of the DIA Greater China team, deepening our understanding of the R&D gaps and areas of need in innovative Chinese companies, closely working with government agencies such as CFDA, and actively looking for other partnerships or collaborations that will help DIA strengthen our contribution to China, immediately come to mind.

I strongly believe that DIA truly is an essential partner in catalyzing knowledge creation and sharing to accelerate health care product development. I also think it is important, in alignment with DIA's global strategic themes – converge, connect and convene – to drive thought leadership through collaboration; to connect the global health care products community; and to become the indispensable voice for innovation.

AG: The China FDA is currently implementing a series of regulatory reforms for ensuring clinical trial data integrity, encouraging innovative product development, and other purposes. What are your views on these goals, and where/how can DIA collaboratively work to help achieve them?

CZ: On August 18, 2015, the China State Council released an official order on Drug Review, Approval and Innovation. Since July 2015, CFDA has engaged with both domestic and multinational pharmaceutical companies on data integrity self-check and inspection. Inspection schedules and findings are made public, attracting huge attention and causing some uncertainty within the pharmaceutical industry. These governmental actions are expected to help reduce the backlog of drug applications, improve the overall quality of drug applications, especially with regard to clinical data (for new drugs and generic drugs, as well as medical devices).

AG: This October, you will present our second annual *DIA China Drug Discovery Innovation and Exhibition.* Many observers called the first conference and exhibition, in 2015, the most comprehensive and in-depth conference of its kind. What are the major topics this upcoming conference will address, and how have these topics evolved since last year's debut offering?

CZ: Drug Discovery Innovation is an exciting new area for both China and DIA, and our primary objective is to tap into, identify, and collaboratively meet, the needs for knowledge growth in this area. The conference will have 6 themes and 12 sessions; it will cover the early stage of pharmaceutical R&D. The contents will include target selection/validation, lead compounds identification/optimization, IND enabling studies, IND application management, China-based early- to mid-stage clinical development and business development & partnering. The conference will be a productive platform for domestic innovative pharmaceutical R&D professionals to learn and share their knowledge and experience. The 2015 conference on this same topic was a huge success in terms of both attendance and the high caliber of content; I am certain that this year's version will build on that success and deliver even greater value to participants, reflecting the rapid progress underway in China in the drug discovery field.

AG: Finally, what message would you like to share with DIA's member and volunteer network in China?

CZ: I am grateful to the many people who have contributed in the past decade to the growth of DIA in China. Without the support and dedication from the ACC, our program committee members, speakers, collaborators, and partners from CFDA, it would not have been possible for DIA to convene such dynamic ideas, voices and programs as the *DIA China Annual Meeting,* our *DIA China Drug Discovery Innovation and Exhibition*, and other training programs. We are DIA and DIA needs your support!

DIA APPOINTS NEW MEMBERS TO BOARD OF DIRECTORS
Industry Experts to Strengthen DIA's Impact Around the World

Washington, DC – DIA, the premier professional community and knowledge exchange network for global health care product development, announced today its election of four new members to its Board of Directors.

Newly appointed members include:

- **Joseph Scheeren, PharmD**, Head of Global Regulatory Affairs, Pharma and Consumer Care, Bayer Healthcare
- **Jonathan Sheldon, PhD**, Global Vice President, Healthcare, Oracle Health Sciences
- **Jeffrey S. Payne, CPA**, Chief Financial Officer, Picwell Inc.
- **Lingshi Tan, PhD**, Chairman and Chief Executive Officer, dMed Company Limited

"With shifts in the environment toward targeted, personalized treatments to improve patient care, it is apparent that the old paradigm of drug development is no longer sustainable," said Barbara Lopez Kunz, Global Chief Executive, DIA. "There is still much to be done to advance the personalized model of care and, with the addition of these industry experts, our leadership team will continue to strengthen DIA's ability to take innovation to scale and increase our impact around the world."

As part of their responsibilities, the new board members will help the DIA to:

- Define the future innovative offerings delivered through DIA's knowledge platform for new stakeholder value.
- Sustain and enhance DIA's globalization model for engagement/and escalation with appropriate financial and non-financial milestones.
- Re-imagine the DIA governance model and the transition plan for the future.
- Support DIA's vision via strategic relationships with visionary, like-minded organizations to multiply DIA's impact on health.

"We are pleased to welcome the new members to the DIA Board of Directors and look forward to their expertise to continue advancing innovation worldwide; underscoring DIA's vital role in generating new knowledge across the globe," Kunz said.

Meet the DIA Board of Directors.

DIA's podcast series, *Driving Ideas to Action*, offers listeners a unique opportunity to hear directly from leaders in health care product development. Click the links below or subscribe to our *Driving Ideas to Action* iTunes podcast channel to stay connected.

OUR MOST RECENT PODCASTS:

US: PDUFA VI: FDA's Woodcock and Mullin Review and Preview the Reauthorization

The current US Prescription Drug User Fee Act, commonly referred to as PDUFA, V, will sunset at the end of 2017. At the first Public Meeting on PDUFA Reauthorization, Center for Drug Evaluation and Research Director Dr. Janet Woodcock said, "PDUFA has been generally considered successful. We continue to meet or exceed nearly all our application review goals…And these accomplishments are, in part, made possible by the resources provided by this program." In this exclusive podcast, Dr. Woodcock and Dr. Theresa Mullin, Director of FDA's Office of Strategic Programs, discuss PDUFA, the need for reauthorization into PDUFA VI, and its progress since the initial 1992 legislative authorization.

Listen Here.

Clinical & Real-World Data: Is AI the Missing Link?

The world's first regulatory-approved artificial pancreas proves the powerful potential of machine learning, as it informs the algorithm regulating real-time insulin delivery as a function of the patient's blood sugar level. Where else can machine learning or artificial intelligence (AI) help to drive health care innovation? Dr. Joelle Pineau, Associate Professor at the School of Computer Science at McGill University, Co-Director of the Reasoning and Learning Lab, and member of the Centre for Intelligent Machines, explains how AI can improve the operational and scientific efficiency of clinical trials, advance personalized medicine and cancer research, and previews the Keynote Address, *The AI Revolution: Perspectives on Health Care in the Information Age*, that she will deliver at ***DIA's Canadian Annual Meeting 2016***.

Listen Here.

"Biosimilars have at last come of age in the United States"

While they do not present new treatment options, biosimilars make tried and trusted, highly effective but very expensive biological cancer therapies more widely available at a more affordable price. With their potential for improving access to effective biological therapies through reduced costs, biosimilars have garnered great interest among industry, regulators, patients and payers. Program Chair Cecil Nick, who has worked for more than three decades in clinical development and regulatory affairs, explores the science, global regulatory pathways, clinical evidence for and other aspects of biosimilars that will be discussed at DIA's ***Biosimilars 2016 Conference***.

Listen Here.

Mission, History & Opportunity Attracts New DIA Americas Leadership

In August 2016, DIA welcomed Dr. Sudip Parikh as Senior Vice President and Managing Director for the DIA Americas region. Dr. Parikh previously served as Vice President and General Manager of Health and Consumer Solutions at Battelle; he has also served as senior liaison for the US Senate Appropriations Committee in budget negotiations with the pharmaceutical and biotechnology industries, and research universities, centers and hospitals. What was the most important lesson he learned while working on Senate Appropriations? "At the biggest level, it's never let the perfect get in the way of the good," he explains. "There are many, many stakeholders at the table, and the perfect IS the enemy of the good."

Listen Here.

WRITE TO BE READ

How to Produce Industry Content That Professionals Will Actually Read

Christopher G. Kelly, MEd

When people hear the term "health literacy," most envision patients struggling to find and digest information about their own health care needs. But health literacy principles also apply to physicians and other industry professionals who rely on journal articles, conference posters, research reports and other materials to understand ongoing trends in their field.

Professional literacy is the degree to which individuals have the capacity to obtain, process, understand, and act on complex, scientific information needed to make appropriate clinical or health system decisions. According to a **2015 survey**, physicians spend an average of nearly six hours per month reading medical publications, and review an average of four journals per month. Fully 60 percent of them regularly or often use peer-reviewed journals as a source of continuing professional development.

These materials have significant impact on their careers and the patients they serve. A report published in 2014 shows **16 percent of physicians reported saving a patient's life** in the previous year due to news they read in medical literature, and nearly 75 percent said they change their clinical practices quarterly or monthly based on reading these materials.

SO MUCH TO READ, SO LITTLE TIME

The goals of most health care publications, scientific posters and other material is to communicate relevant information and context to enable appropriate clinical decisions and stimulate research while establishing a peer-reviewed evidence base. Yet these goals can sometimes conflict with needs of busy health care professionals. Anyone who has ever tried to scan a peer-reviewed scientific journal knows how difficult it can be to find a specific piece of information, or to get an overall sense of an article.

Common barriers such as time constraints, fatigue, the desire to skim for information, and an overload of information can further impact a professional's ability to select and process the valuable content offered through these publications. And as they **transition from print to mobile device formats,** these barriers may only get worse.

These obstacles can be counterproductive for authors and readers, both of whom benefit from content written and published in a way that is easy to comprehend. Authors who produce material that is engaging and digestible are more likely to garner a broad audience and to provide readers with a clear understanding of their work and message, and readers are able to absorb those messages more readily so they can apply them in their work.

The good news is that we can leverage the same best practice guidelines that drive clear communication in patient-focused health materials for professional literature:

- **Use active voice, concise sentences, and shorter paragraphs.** Many authors use passive voice due to the perception that it sounds more "objective" or "scientific." Active voice, however, sends a stronger and more concise message that enhances clinical relevance. Developers of writing guidelines, including those in the AMA Manual of Style and many scientific journals, have recognized the need to improve readability, and have specified the use of active voice in most instances. For example, even a simple modification from the passive "it was concluded that" into "we concluded that" or "evidence suggests that" can reduce awkward sentence structure and bring focus onto the conclusion itself. This tone also drives confidence in the source and motivation to stay engaged with a publication. It is also important to break down longer, narrative passages into smaller paragraphs to give readers a chance to transition their thought from one concept to the next. This is called "chunking" content and offers a rest for the reader. Authors can also ensure that the material is understood by summarizing key takeaways in a short paragraph or listing. This is particularly important when closing a longer publication and ensures that the reader retains key takeaways and desired actions.
- **Follow a consistent format throughout.** Using consistent design elements (such as colors, fonts, headers, subheaders, and bullet patterns) offers consistent structure that enable readers to scan, orient and move smoothly through pages. These elements serve as "road signs" and help readers to find the information that is most relevant to their needs. It is also important to apply formatting to the text itself, such as keeping a consistent

About the Author

Chris Kelly, *associate director of Medical Communications, co-leads the medical writing team for the Health & Engagement Communications organization at QuintilesIMS. With more than 25 years of medical communications experience, Chris has provided direct patient care, health education, professional training and instructional design in a variety of healthcare and medical communications settings.*

order of comparisons (e.g., results for product A followed by product B) and figures (e.g., product A to the left of product B on all bar graphs).

- **Use white space to improve readability.** Maintain adequate white space including margins, spaces between columns, and before and after headings to provide a visual rest for the reader and to prevent the document from looking cramped or crowded. Authors may need to reduce the amount of content to allow for adequate white space.
- **Include charts, graphs, bulleted lists and informative subheads to break-up content.** Charts, figures and illustrations not only serve to break up content, but are especially effective at conveying certain types of information. These elements are particularly useful when attempting to enhance the processing and understanding of complex concepts. For example, a table may be the most efficient way of visualizing large amounts of data, while a figure may be best at conveying a key finding or focused concept.
- **Choose fonts, font sizes, and color schemes that make content easier to read and understand.** Use the appropriate type style to facilitate easy reading. For example, serif type (font has additional markings at the end of characters, such as Times New Roman) facilitates easier reading of text passages due to character recognition, while sans serif (without additional markings on characters, such as Arial), are preferred for titles and headings as well as smaller captions for their clean lines and ability to stand out. The choice of font may also influence size needed for readability. Use uppercase and lowercase letters for text and most headers to improve tone and readability. Using all capital letters not only convey a tone of "shouting," but are more difficult to read. While color may add aesthetics to a presentation or document, the primary purpose of color in a scientific work should be to convey information most effectively. Choose a color scheme that utilizes contrasting colors and highlights differences in text sections and data without adding distractions.

Submission guidelines and required styles for some scientific publications can make it difficult to incorporate all of these health literacy guidelines, but even small changes can have an impact. Whether you are producing a peer-reviewed article, news story, blog post, or an industry presentation, writing with a clear purpose and creating content designed with the reader's needs in mind will make it easier for your audience to engage with your work, and for you to share your knowledge with your peers.

PATIENT ENGAGEMENT: SO WHAT'S IN IT FOR PATIENTS?

Patient engagement in therapeutic product development has moved into a new era, advancing from "Do we really want to do this?" to "How do we get this done?" Several *DIA 2016 Annual Meeting* sessions addressed the topic of patient engagement, including the thought-provoking and truly global panel discussion of *Patient Involvement Today and Tomorrow: What's In It for Patients?*

Panelists (see accompanying list) agreed that the global synergy, in particular between the US and EU, we see on patient-focused drug development across numerous industry, regulatory and patient advocacy initiatives, must continue to provide solid and scalable platforms for further engagement.

Graeme Johnston began the discussion by presenting his perspective as a patient who survived a cancer scare in 2001 and was diagnosed with rheumatoid arthritis (RA) in 2006. He described what it's been like to live with RA, specifically its frequent debilitating inflammation and fatigue, for more than a decade, and his patient engagement experiences at both the local and national levels in the UK.

Isabelle Moulon also reported from Europe, using the EMA's recently-published (May 2016) **2015 Annual Report** as one of the bases for her remarks. This Report illustrates the multiple avenues that patients have to contribute to industry and regulatory collaborations and other patient engagement initiatives in the EU. For example, she explained, patient representatives now serve on the EMA management board and scientific committee, and formally contribute to product life cycle management and post-authorization efforts. In addition, agency planning discussions for a specific disease or therapeutic area now include a patient representative who is expert in that disease or area.

Isabelle also stressed the importance of training and knowledge in effective patient engagement: Not only deep knowledge of the disease and its underlying science, but deep knowledge of the drug development and regulatory review and approval systems. To effect change within the EU's industry and regulatory systems, a patient must have more than just good intentions. To this end, the **EUPATI Toolbox on Medicines R&D**, released in early 2016 by the European Patients Academy through the Innovative Medicines Initiative (IMI), has provided training and tools which have transformed patient advocacy and engagement in the EU.

Graeme suggested that patient advocacy and engagement must be strategized on a global level to align with and meet the needs of the global drug and device product development ecosystem, and begin as early as possible in the discovery process to maximize its benefits to industry and patients. He also wondered if we had reached the time to convene an "ICH for Patient Engagement."

Theresa Mullin's view from the Americas shared Isabelle's perspective on the importance of knowledge and training which can transform well-intentioned patients into system-savvy experts who know how, where, and with whom to share expertise on their particular disease. She specifically addressed the issue of labeling: Too often, products are developed according to what doctors or other medical professionals think patients want for their specific condition, not what patients actually want; too often, because they were never asked, the resultant products don't address these patients' chief complaint.

All speakers agreed that creating best practices and processes for patient engagement and advocacy are necessary, but not enough to for the cultural change that must take place in and between patient, industry and regulatory organizations to effect true, and truly effective, patient engagement in drug development. Too often, patients wait for an invitation, which may or may not be extended, to contribute. And even when invited, where at the table do patients want to sit?

Mary Murray (Associate Director, Diversity & Patient Engagement, Bristol-Myers Squibb Company) and DIA Global Director of Engagement Elizabeth Lincoln addressing the DIA 2016 Annual Meeting Patient Fellows.

DISCUSSION PANELISTS:

Chair Marc M. Boutin, JD
CEO, National Health Council

Lode Dewulf
Vice President & Chief Patient Affairs Officer, UCB, Belgium

Anton Hoos
Head of Medical Affairs, Amgen GmbH

Graeme Johnston
Advisory Board Member, Patient Focused Medicines Development, UK

Isabelle Moulon, MD
Head of Patients & Healthcare Professionals Department, EMA, EU

Theresa M. Mullin, PhD
Director, Office of Strategic Programs, CDER, FDA

Bettina Ryll
Founder, Melanoma Patient Network Europe

THE DISCONNECT: Clinical Trials and Real-World Side Effects

Keith Hoffman, PhD

Due to financial and logistical hurdles, no pre-approval clinical trial can ever be large enough, or long enough, to identify and properly characterize all side effects that may occur once a drug is introduced to large patient populations. Indeed, side effects from drugs, vaccines, and devices approved by FDA are a major public safety concern. **Approximately 1,500,000 Adverse Drug Events (ADEs) are currently reported to FDA each year, across all approved drugs.**

A member of the FDA's Office of Drug Safety has explained that: 1) "the complete adverse event profile of a drug is not known at the time of approval because of the small sample size, short duration, and limited generalizability of pre-approval clinical trials" and, 2) "since most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications suspected of interaction with the study drug, the studies' participants may not be representative of the real world where the drug is eventually used."

Such side effects do not occur only when consumers take these medications at home, away from their doctor's watchful eye. ADEs occur in almost 7% of hospitalized adult patients. ADEs are between the fourth and sixth leading cause of death in the US. In short, all FDA approved drugs have the potential to trigger various side effects not revealed during pre-approval investigations.

CAREFUL AND CONTINUOUS POST-APPROVAL MONITORING IS THEREFORE VITAL TO THE EVALUATION OF A DRUG'S SAFETY PROFILE

To increase the likelihood that drug efficacy signals can be detected during clinical trials, pharmaceutical developers purposefully enroll subjects who are expected to help achieve the best possible results. Potential clinical trial participants are subjected to rigorous inclusion and exclusion criteria. Because of this selection process, subjects who ultimately are enrolled in the trial are a relatively homogenous group.

This selection process is vital for determining a compound's efficacy and also is usually necessary for financial and logistic reasons. The downside of this process, however, is that this homogeneous group of subjects may react in similar ways to a test drug. Clinical testing typically uncovers common side effects such as gastrointestinal discomfort, flu-like illnesses, nausea, etc. However, serious and life-threatening side effects that did not surface during the screening programs often become evident only after the drug wins regulatory approval. This is a global issue.

Therefore, the clinical trial process cannot uncover many of the side effects that occur once the drug is introduced to real-world, heterogeneous patient populations that were not subjected to such inclusion and exclusion criteria. Consumer populations will have a wide range of comorbidities, polypharmacy, race, gender, and age differences, etc., that the pre-approval drug could never have been comprehensively tested against.

THE GRADUAL EVOLUTION OF SIDE EFFECT PROFILES ACROSS NUMEROUS DRUG CLASSES AFTER THEY WERE APPROVED UNDERSCORES THE PRECEDING POINTS

Health care professionals routinely obtain safety information from drug label "inserts" that are often based predominantly on pre-approval clinical trial results. It is this reliance on incomplete safety data derived from limited clinical trial systems that creates a significant gap in knowledge for the health care industry.

HOW ARE POST-APPROVAL ADE DATA OBTAINED?

FDA professionals and pharmacovigilance experts routinely look to FAERS (FDA Adverse Event Reporting System) data as both a guide to, and signal generator of, drug safety issues. Both groups employ a wide array of sophisticated data mining and signal detection techniques. FDA uses such analyses to issue warnings, mandate label changes, and remove drugs from the US market after the incidence or severity of their side effects is determined to significantly differ from what clinical trial results previously suggested.

Unfortunately, FAERS has remained largely inaccessible to health care professionals. In fact, publicly available FAERS information can only be obtained through complicated data downloads by individuals familiar with relational databases (FDA states that a simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases) or through burdensome Freedom of Information Act (FOIA) requests.

HOW DO PROVIDERS GET THEIR SAFETY INFORMATION?

Many doctors keep up to date on drug safety – especially regarding the drugs they typically prescribe – by reading scientific publications, attending meetings, conferring with pharmacy specialists, and trading safety notes with other doctors. However, it is widely recognized that most doctors and providers simply do not have the time to scour the literature and attend the multiple conferences that could keep them continuously informed about the ever-changing world of drug safety.

Indeed, time and information-overload constraints force many health care providers to obtain safety information from sources that may be significantly biased (pharmaceutical sales representatives) or have limited influence (FDA alerts).

FDA ALERTS

FDA regulatory advisories such as their "Safety Alerts" are meant to update consumers and practitioners about new side effects (not already disclosed in the drug's safety labeling) that have emerged in post-marketing use. FDA Safety Alerts can take many forms. Most are warnings about a new side effect and may include FDA-mandated label change(s). Serious Alerts include "Black Box" warnings, product withdrawals, and recalls. In general, the seriousness of the alert corresponds to the size of the impact.

About the Author

Keith Hoffman *was a member of the founding management team of Advera Health Analytics and served as the Company's Vice President of Scientific Affairs for six years and is now an active Scientific Advisor to Advera. Keith has 20 years of science, business, and intellectual property development experience in the biotechnology, pharmaceutical, and consumer goods industries.*

Any FDA Alert can have a significant impact on a drug and its manufacturer, including changed prescription behavior and declining sales. As in most areas of risk communication, warnings and alerts are most effective when they are specific, offer alternative options, and are repeated. The literature suggests that the effectiveness of FDA alerts mirrors these same general risk communication guidelines – i.e., alerts produce results when they are specific and actionable.

CLEAR AND ACTIONABLE POST-APPROVAL DRUG SAFETY INFORMATION

There is an obvious need to enhance the efficient use of post-approval ADE data to address the above-described deficiencies associated with both the clinical trial system and currently available drug safety information.

Major changes need to be made in how post marketing drug safety data are: 1) cleaned, organized and accessed; 2) made actionable for relevant health care industry participants; 3) correlated to actual medical costs; and, 4) utilized for predictive signaling.

Recent studies have documented the utility of FAERS for generating safety signals, while other investigations have compared FAERS data with ADEs from clinical trials and population studies. The benefit of using FAERS data to fill information gaps left by pre-approval safety testing is clear. However, current access to FAERS depends on proprietary data mining and signaling tools used by regulatory agencies and major pharmaceutical companies. These systems are expensive, inaccessible, and complex, which effectively eliminates their use by most health care professionals. Additionally, publicly available FAERS information can only be obtained through complicated data downloads by individuals familiar with relational databases.

Even when health care professionals go through the steps to download FAERS data, they are then faced with a host of accessibility issues. FAERS has over 200,000 separate identifiers for the approximately 4,100 drugs in the database. If you do not know all the name variants for a given drug, you will not be able to download all the case reports associated with it. For example, Lipitor (atorvastatin) has 1,762 separate name designations in FAERS; Tylenol (acetaminophen) has 2,421. Furthermore, case reports submitted to FDA often have spelling errors and misclassifications, with various data points either missing or inadequately reported. Many are frequently duplicated. FAERS needs to be scrubbed and organized in a way that makes it accessible to a much wider array of industry players.

Thousands of people every day count on objective product ranking and scoring platforms such as *Consumer Reports* to guide their purchasing decisions. Drug products have no similar platform for efficacy or safety. The development of safety rankings for drugs would be a positive step in making adverse event information accessible to and actionable by health care providers. Furthermore, postmarketing ADE data are a vital component of drug safety and must be more widely accessed and analyzed by the health care community.

Determining a drug's overall safety risk necessarily involves the simultaneous assessment of several safety related parameters. Choosing these factors and determining how to weigh their individual contribution within a ranking platform needs careful consideration. A drug safety ranking system of this type could meet a significant unmet need in the medical and health care communities by helping to bring ADE discussions to the forefront of prescribing, formulary, and insurance decisions.

A system to estimate real-world costs associated with adverse events triggered by a given drug could meet this need by analyzing the direct medical costs of downstream care for patients who suffered an ADE. A quantitative metric for these downstream outcome costs would give managed care professionals a much needed tool to enable informed decisions about which drugs to include or exclude from formularies and coverage.

A signaling method is also needed in order to predict when FDA will, or should, issue a postmarketing Safety Alert on a drug. Signaling would only be useful if it focused on ADEs in which FDA has already demonstrated interest. A system of this type must quantify past FDA Alerts to predict similar future actions. Given the limitations regarding FAERS reporting rates, signaling would ideally be driven by disproportionality measures.

While we have recently developed new signaling methods for FDA alerts and for estimating drug safety risks by ADE cost analyses, more work needs to be done. If the health care industry can supply more solutions to the shortcomings of 1) the clinical trial process; 2) the dissemination and accuracy of drug safety information; and, 3) the non-accessibility of FAERS, a new age of informed drug safety decision making will benefit us all.

References available upon request.

Your Future Career Awaits

Join us for DIA's Complimentary Virtual Career Fair on November 9, 12:00-3:00PM.

DIA's Virtual Career Fair is your opportunity to connect online and in real time with employers and recruiters and explore a variety of open positions.

Let us help you to propel your career.
DIAglobal.org/careerfair

DIA