Pharmacovigilance and Risk Management Strategies
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The Pharmacovigilance and Risk Management Strategies Conference included thirteen sessions that describe the current regulatory environment as well as primary sources of risk. The sessions, together with a keynote talk by Steven Murray (*Exponent*), provide a foundation for making informed and up-to-date decisions in a pharmacovigilance program.

Key Takeaways

- New ICH and CIOMS programs are underway to address evolving issues related to patient engagement and safety data collection.
- The global regulatory framework for pharmacovigilance has developed in different regions independently and consequently exhibits a regional focus on different areas of safety and pharmacovigilance practice.
- The regulatory context surrounding risk management tools, such as REMS and RMPs, continues to evolve in a regional manner, making global risk management a challenging endeavor.
- Current research findings on topics such as DILI and alloCAR-T therapies will have an impact on the benefit-risk analysis associated with these therapies.
- Several pharmacovigilance approaches are being pursued to help address the growing concern of medication errors.
- Regulatory safety assessment is making growing use of real-world evidence using novel approaches.

ICH and CIOMS Updates
Michael Richardson (Bristol-Myers Squibb) described the Council for International Organizations of Medical Sciences (CIOMS) as a think tank that takes on "gnarly pharmacovigilance topics" and produces guidelines. Currently, CIOMS is organized into six working groups. Of particular interest, Working Group XI is focused on patient involvement in the development and safe use of medicines. The final expected guidelines from this group will take the form of a pragmatic *Points to Consider* document that describes the current state of the field, existing initiatives, and upcoming challenges.

One of the significant users of CIOMS guidelines is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which often uses the CIOMS guides as a basis for their own guidelines. An update to their E2D Guideline for post-approval safety data management is currently in the works (E2D(R1)) to better use existing data as well as to capture new data, such as social media, that were not available when the guideline was first created.

Regional Update on Regulatory Framework
Asia
India's pharmaceutical market is experiencing a 12-14 percent growth per year. Along with this market growth, there is a concomitant growth in pharmacovigilance requirements for market authorization holders in India, according to J Vijay Venkatraman (Oviya MedSafe). In Japan, labeling regulations have been revised for the first time in twelve years. Rie Matsui (Pfizer) provided a detailed summary of the revisions and how these changes are currently in a transition period for the next four years. Finally, China has been accelerating its pace in regulatory reform to follow ICH guidelines, following joining the ICH in 2017. Stella Xu (dMed) described the implementation plans and standards that China is establishing, in particular the updates to the E2B(R3) specification for electronic submission of post-marketing safety reports.

Europe
With Brexit looming, the practical ramifications of what a UK withdrawal means for European pharmacovigilance is a hot topic. These effects include administrative changes, such as moving the headquarters of the European Medicines Agency (EMA) from London to Amsterdam. But withdrawal also has potentially patient-impacting consequences, such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA) losing voting rights in EU regulatory decision-making processes. Sarah Vaughan (MHRA) described how the UK will continue to focus on patient health after the implementation period and discussed the initiation of several pharmacovigilance approaches, including a Yellow Card Biobank.

The EMA partnered with the Heads of Medicines Agencies, creating a task force to create recommendations for how to benefit health using Big Data. Hans-Georg Eichler (EMA) presented the first steps in establishing funding to execute the plan laid out in the priority list generated by the task force. This will involve a cross-EU federated platform to permit queries on data across the different Member States.

North America
Sophie Sommerer (Marketed Health Products Directorate) described various changes as a result of Vanessa's law in Canada:

- Confidential business information can now be publicly released if there is a public health reason.
- Hospitals must report all serious adverse drug reactions.
- Biologics naming requires a non-proprietary active ingredient identification.

Gerald Dal Pan (Food and Drug Administration, FDA) presented that US adverse event reporting appears to be leveling off from its steady increase (as measured through the FDA Adverse Event Reporting System, FAERS). FAERS II is underway, which will allow receiving ICH E2B(R2) and (R3) safety reporting. The FDA has a five-year strategic plan for updating Sentinel, FDA's medical safety surveillance system. This includes incorporating more diversified data as well as adding advanced analytics to support better signal detection. Steven Anderson (FDA) presented a broader look at active surveillance at the FDA in general. This includes incorporating more data, more analytics, and pilot studies into the use of artificial intelligence to help automate reporting.

In-Depth Look at RMPs and REMS
Risk management is the concept of ensuring that the potential benefits of a medicine exceed the potential risk. Although this principle is shared across both the US and the EU, the actual implementation can vary considerably. In the EU, the EMA always requires sponsors to submit a Risk Management Plan (RMP) document for each drug being reviewed for approval. However, in the US, the FDA requires a similar document, a Risk Evaluation and Mitigation Strategies (REMS), only if deemed necessary. Similar differences exist at the level of safety assessment.

Catherine Baldridge (Essential Pharmacovigilance) described factors that the FDA considers when determining if a REMS is required. And, significantly, she also discussed one factor that the FDA does not consider: the capability of a company to actually produce a satisfactory REMS. Various options exist for a company to meet this requirement, from building an in-house REMS department, hiring a CRO, to using external vendors. Regardless of the method selected, a company requires an appropriate budget and effective leadership that can make the appropriate organization changes needed to successfully implement a REMS program in a time crunch.

The case of thalidomide serves both as a practical example of the need for a risk management system and how a global strategy can be effectively built. In the 1950s, thalidomide was used as a sleep aid to reduce morning sickness in pregnancy. It would later be found that a single dose given 20-36 days after fertilization was sufficient to cause congenital malformations. 12,000 infants would be born with birth defects before this drug was withdrawn from the market. However, subsequent research into thalidomide found it effective for use in erythema nodosum leprosum and multiple myeloma. Paul Sheehan (Celgene) described the core principles of Celgene's risk management program to safely deliver thalidomide to patients while minimizing the evident risk. The company developed three different pregnancy prevention models that are selected and then tailored to the country-specific needs. The patient safety outcome of a million patients having been treated in 80 countries with zero children born with congenital abnormalities has served as evidence of the efficacy of a risk management plan in minimizing risk.

Current Research on Mechanisms and Their Impact on Assessing Risks
Drug-Induced Liver Injury (DILI) is the most frequent reason for drug withdrawal, restriction, and modification of labeling. According to Hervé Le Louet (CIOMS), DILI is a growing problem that is responsible for more than ten percent of all cases of acute liver failure.

There are multiple challenges associated with addressing DILI. Currently, no tests are available to diagnose DILI directly. It remains an exclusion diagnosis, with an invasive liver biopsy being the gold standard for studying the pathophysiology. Even with a diagnosis, expert opinion during case review is the best assessment method, as no validated assessment scale is available. In addition, we currently lack predictive models to identify the risk of DILI pre-clinically. Research is underway to help discover and qualify new biomarkers as well as to identify potential genetic risk factors that may indicate DILI susceptibility.

Another promising therapy is the use of T cells that have been genetically altered to express a chimeric antigen receptor, CAR-T cells. Peter Bross (FDA) presented a history of T cell therapies starting with clinical studies in the 1990s and culminating in the first FDA approval of two CAR-T cell therapies in 2017. Almost all patients who received CAR-T cell

treatment develop a condition known as cytokine release syndrome (CRS)—so much so that the presence of CRS is used to indicate that the therapy is working. Neurological toxicity is another associated outcome with a poorly understood mechanism. The severity of CAR-T cell toxicities led the FDA to require a REMS for both products to be approved. As new iterations of these cell-based therapies come down the pipeline, the benefit-risk equipoise will continue to remain a challenging pharmacovigilance issue.

Finally, Barbara Morollo (Corbus Pharmaceuticals) presented regulatory issues related to the endocannabinoid system (ECS). Various drugs either mimicking or manipulating the ECS have been developed. These drugs range from preclinical to postmarket stages. The US considers cannabis, a modulator of the ECS, a Schedule I controlled substance, which presents various regulatory challenges during clinical development due to the Federal Analogue Act. Practically, clinical investigations are required to maintain a separate licensure, secure drugs, maintain a chain of custody, and are subject to audits and inspections. The history of ECS drug development presents a look at the unique regulatory challenges present with drug development, both preclinical and clinical, when using controlled substances.

Medication Errors

Medication errors are preventable events that can lead to medication misuse but do not necessarily result in an adverse event. Medication error in the US has an estimated annual cost of nearly $21 billion and is responsible for an estimated 7,000 deaths, according to a study by the Network for Excellence in Health Innovation. Christina Michalek (Institute for Safe Medication Practices) pointed out that medication errors have a significant impact on healthcare providers, in addition to the primary victim.

Jo Wyeth (FDA) presented several approaches for medication error pharmacovigilance. Starting at preapproval, a premarket review can help identify issues before the medication even enters the market. Similarly, postmarket changes need to be considered in the context of the entire product lifecycle. For example, different dosages and formulations may benefit from different packaging. Finally, the entire reporting infrastructure needs to be evaluated to ensure that reports are completed accurately and that reporting itself is encouraged. Achieving medication error prevention through these approaches will require a collaborative effort between patient safety organizations, standard-setting organizations and regulators.

Use of Real World Evidence (RWE)

Real-world data (RWD) includes data related to patient health and delivery of healthcare that is routinely collected, such as in an electronic health record. In contrast, real world evidence (RWE) is evidence generated from RWD related to the usage of drugs, such as potential benefits and risks.

RWD is generated throughout the drug development lifecycle, from discovery through lifecycle management. As Andrew Bate (GSK) put it, RWD is varied. Healthcare databases that contain RWD come from different countries and have different characteristics depending on how they were collected. Careful attention must be given to these factors when selecting sources of RWD for evidence generation.

The regulatory perspective of RWE has shifted. Since 1962, the FDA has been required to determine the effectiveness and safety of a drug based on substantial evidence. This is typically done through the use of externally controlled studies. In 2016, Congress signed into law the 21st Century Cures Act, which mandated that the "FDA shall establish a program to evaluate the potential use of real world evidence." As David Martin (FDA) pointed out, there is value in the regulatory use of RWD and RWE, including the inclusion of a more diverse patient experience compared to a traditional Phase 3 clinical study. However, there remains a regulatory concern that the use of RWE may lead to a false conclusion about a drug's effectiveness without the process of a clinical trial.