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***DIA 2014 50<sup>th</sup> Annual Meeting***

***Celebrate the Past – Invent the Future***

**June 15 – 19, San Diego (CA) Convention Center**

***Session 221 – Benefit-Risk Throughout the Life Cycle: How Should Benefit-Risk Be Evaluated and Communicated from Development through Marketing as New Information Emerges?***

Evaluation and characterization of the benefit-risk balance is a crucial piece for drug approval yet some issues remain ambiguous. Three speakers representing three different ICH regions discussed tools to address these important areas of *Benefit-Risk Throughout the Life Cycle: How Should Benefit-Risk Be Evaluated and Communicated from Development through Marketing as New Information Emerges?*

William W. Gregory, PhD (Senior Director, Worldwide Safety & Regulatory, Pfizer, Inc.) examined how the patient-prescriber interaction can improve the communication of new benefit information in the context of risks. As the evidence base increases from product launch, new risk information continues to accumulate and is easy to find, but information about new benefits is often masked or hidden. Fortunately, several sources of “new” benefit data include trials for new indications, investigator-initiated trials, pragmatic studies and more

systematic analysis and publications. Initiatives such as Clinicaltrials.gov, eMC (electronic Medicines Compendium) by the European Medicines Agency / Medicines & Healthcare products Agency of the UK (EMA/MHRA), and Medline Plus by US National Institutes of Health, make navigating these evidence bases easier. The OpenFDA initiative offers public access to millions of adverse events/medication errors in a dataset that software developers can use to analyze and identify potential safety insights. The American Society of Clinical Oncology (ASCO) provides valuable information, such as algorithms to determine which treatment at which cost is most beneficial to a patient, to patients and oncologists.

FDA has also released two guidance documents on off-label use communication. They recommend that physicians not base judgment on anecdotal or preliminary scientific data because such safety/effectiveness claims are often not demonstrated, and further recommend that companies be truthful, non-misleading, and non-promotional when responding to unsolicited off-label information requests. Dr. Gregory also stated that we often create a fog index for patients which obscures the approved safety information in documents such as the SmPC (summary of product characteristics), US package insert, and medication guide/patient information leaflet; he stressed the importance of using lay language (without medical jargon) to ensure clear, two-way discussion on the benefits, risks and uncertainties of medicines.

Rebecca Nyquist, PhD (Senior Expert Medical Writer, Novartis Pharma AG, Switzerland) focused on harmonizing the benefit-risk message in regulatory

documents at various developmental stages. She recommended aligning this benefit-risk message with the health authority's need for benefit-risk assessment from the early development stages, using a simple framework to simplify updates to the benefit-risk profile, and prudent use of tables/figures. To facilitate this framework, the EMA is piloting an effects table and the FDA is introducing a benefit-risk grid for reviewers; even though they present different approaches, both select main drivers of benefit-risk balance, look for quantification of key benefits/risks as evidence, and ultimately promote more transparent and rational communication of information.

Dr. Nyquist explained that although there is guidance from health authorities on communicating benefit-risk assessment, such as ICH E2C (R2) and ICH M4E, instructions on how to characterize benefit-risk are very limited. She proposed a simplified benefit-risk framework, broadly described as defining the context, identifying key benefits-risks, obtaining and analyzing data, and communicating results. Her recommendations to harmonize the benefit risk message in the Clinical Overview (Section 6) and Periodic Benefit Risk Evaluation Report (Section 18) include:

- Explicitly state and justify key benefits and risks
- Show the magnitude of key benefits and risks in tables/figures
- Show confidence intervals and discuss uncertainties and limitations
- Relate back to the full benefit and risk evidence
- State the position and rationale on benefit-risk balance.

Stewart Geary, MD (Senior Vice President and Chief Medical Officer, Eisai) spoke on the evaluation and use of new benefit information even if it is not indicating a new benefit. Adverse reactions seem to be discovered, and easier to add to approved labels, than new benefit information. This poses the question: What are our expectations for evaluating benefit information? Current standards are rigorous and require such information as comparative efficacy, clinical relevance of effect size, generalizability of treatment response, strength of benefit evidence (statistical rigor, methodological strengths/deficiencies, etc.), and adequacy of dose-response characterization.

In Japan, surveillance studies such as actual use, special use and other clinical studies are usually required for drug approval. Surveillance studies are important because of our need for adverse reaction incident information in real world settings and in high-risk or under-represented patient populations (such as the elderly or those with hepatic or renal impairment), and because a limited number of Japanese patients are actually exposed to a new drug in clinical development. Benefits of these studies include minimal exclusion criteria, large patient numbers, relative cost savings, and capturing real-world evidence. Large study size particularly enhances measuring the quality of life, concomitant medication effects, and relative benefit analysis across various disease subtypes; limitations include no comparison groups, source data verification, and no blinding/randomization. Such studies are conducted in accordance with GPSP (good post-marketing study practice) rather than GCP (good clinical practice). The observational design of these studies results in data that, while useful to clinicians, is more hypothesis than confirmatory.

More data is needed on what constitutes new benefit information and its function in benefit-risk assessments, Periodic Safety Update Reports (PSURs) and patient-prescriber interaction.

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