

Agenda: Workshop on IND Safety Assessment and Communication

Clinical Trials Transformation Initiative

Purpose: "To promote responsible oversight of safety for pre-market drugs consistent with the intent of FDA's new IND safety rule"

February 28 and 29, 2012

Hyatt Regency, Bethesda, MD

Haverford Room

Key Objectives

- Discuss findings from a survey of sponsor practices
- Discuss strategies that companies are using to implement FDA's new IND safety reporting rule
- Discuss the challenges to meeting the intent of the new IND safety reporting rule: What are the gaps between current practice and a premarket safety system optimized to detect and communicate valid safety signals as early as possible?

Day 1 - Tuesday, February 28, 2012 (9:00 am to 5:00 pm)

By the end of Day 1, all participants should submit a list of up to 3 gaps between current practice for oversight of pre-market safety and the intent of the new IND safety reporting rule. In addition, participants are encouraged to submit a list of potential solutions for these gaps. The submitted items will provide the basis for our Day 2 discussions.

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| 9:00 – 9:10 am | Introductory Presentation – Goal of the meeting: Increase understanding of current practice and exchange ideas to optimize oversight of premarket safety within drug development programs

Presenter: Judith Kramer, M.D., M.S. (Executive Director, Clinical Trials Transformation Initiative; Associate Professor of Medicine, Duke Translational Medicine Institute) |
| 9:10 – 9:30 am | Summary of survey results, highlighting those areas where greater clarification is needed

Presenter: Patrick Archdeacon, M.D. (Medical Officer, Office of Medical Policy, Center for Drug Evaluation and Research, FDA) |

Panel Sessions

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| 9:35 – 9:55 am | Panel Session I: Organization of personnel and data (e.g., safety teams, Safety Management Teams (SMTs), Data Monitoring Committees (DMCs), clinical development teams, senior governance committees, safety databases, clinical databases) |
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Panel Presenter: Jose Vega, M.D. (Vice President, Global Safety, Amgen, Inc.)

9:55 – 10:45 am

Panel Session I Discussion

Moderator: Elliott Levy, M.D. (Senior Vice President, Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb)

Panel member: Kamal Shah, M.D. (Head of Global Trials Safety Surveillance, Celgene Corporation)

Panel member: Dan Odenheimer, Ph.D. (Vice President, Clinical Development and Evaluation, Human Genome Sciences)

- Outline approach(es) to organizational structures and the interactions across layers and structures
- Discuss the remits of various roles (safety physician, clinical lead, medical monitor, SMT, DMC, senior governance committees)
- Describe the organization and content of the global safety database and the clinical databases

10:45 – 11:00 am

Break

11:00 – 11:20 am

Panel Session II: Processes and approaches to aggregate safety reviews at the level of a protocol, indication, therapeutic area, and product (database organization, signal detection tools, SOPs)

Panel Presenter: Milbhor D'Silva, M.D. (Vice President, Product Safety & Pharmacovigilance, Astellas Pharma Global Development)

11:20 am – 12:30 pm

Panel Session II: Discussion

Moderator: Milbhor D'Silva, M.D. (Vice President, Product Safety & Pharmacovigilance, Astellas Pharma Global Development)

Panel member: Bob O'Neill, Ph.D. (Senior Statistical Advisor, Office of Biostatistics, Center for Drug Evaluation and Research, FDA)

Panel member: Eric Lewis, M.D. (Safety Development Leader, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline)

- What methodological approaches have proved useful in performing safety analyses across data from multiple trials, indications, therapeutic areas?
- What types of safety issues are amenable to detection with these approaches? What types of safety issues are more difficult to detect?

Are there identifiable “blind spots” in premarket safety signal detection?

- Discuss analytic approaches and/or SOPs used by safety team, clinical team, SMTs, and DMCs. How are they similar or different from one another? How does their access to and use of the safety and clinical databases differ? How do the remits of these various structures differ with regards to product safety issues?

12:30 – 1:30 pm

Lunch

1:30 -1:50 pm

Panel Session III: Signal thresholds and escalation of potential safety signals (e.g., quantitative versus qualitative thresholds, internal escalation, escalation pathways, confirmation of signals, regulatory reporting practices)

Panel Presenter: Janice Wherry M.D., Ph.D. (Group Director, Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb)

1:50 – 3:00 pm

Panel Session III: Discussion

Moderator: Ron Leong, M.D. (Executive Director, Patient Safety, AstraZeneca)

Panel member: David Balderson, Ph.D. (Executive Director, Global Safety Operations, Amgen, Inc.)

Panel member: Christopher Breder, M.D., Ph.D. (Acting Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs, CDER/FDA)

- What challenges have made it difficult for sponsors to implement the new IND safety reporting rule with regards to individual SAEs?
- How are potential signals communicated, escalated, and confirmed?
- What are thresholds for regulatory reporting? What are thresholds for updating reference safety information [Investigator Brochure (IB), Company Core Data Sheet (CCDS) and Company Core Safety Information (CCSI)]?
- What is the best use of supplementary data sources when determining the appropriate disposition to the FDA of a potential signal based on aggregate data?

3:00 – 3:15 pm

Break

- 3:15 – 3:35 pm **Panel Session IV:** Handling of blinded data and analysis of blinded studies (e.g., signal detection, risk benefit decisions, program management decisions)
- Panel Presenter: Christy Chuang-Stein, Ph.D. (Executive Director, Head of Statistical Research and Consulting Center, Pfizer, Inc.)
- 3:35 – 4:45 pm Panel Session IV Discussion
- Moderator: Bob Temple, M.D. (Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research, FDA)
- Panel member: Dave DeMets, Ph.D. (Professor, Department of Biostatistics and Medical Informatics, University of Wisconsin)
- Panel member: Jethro Ekuta, D.V.M., Ph.D. (VP and Head, PV Analytics & Insight, Janssen Research & Development, L.L.C.)
- What are practices regarding unblinding of data related to evaluations of adverse events?
 - The safety rule and guidance clearly contemplate unblinded analyses of some SAEs to look for imbalances in the groups. How can these be detected at all if blind is maintained?
 - Discuss the problems caused by allowing access to unblinded or treatment-stratified data to a) safety teams, b) SMTs, c) internal oversight committees, d) DMCs. What thresholds might limit the need to do this?
- 4:45 – 5:00 pm Closing Remarks: Jose Vega

Please remember to submit your list of gaps between current practice and a premarket safety system optimized to detect and communicate valid safety signals as early as possible

- 5:30 – 7:30 pm Reception

Day 2 – February 29 (8:30 am – 12:00 pm)

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| 8:30 – 8:45 am | Comparing current practice for assessment and communication of premarket safety with the intent of the new IND safety reporting rule:
Perceived gaps and proposed solutions

Presenters: Patrick Archdeacon, Jose Vega, Judith Kramer |
| 8:45 – 10:00 am | Open discussion: Perceived challenges to building a safety system capable of meeting the intent of the new IND safety reporting rule. |
| 10:00 – 10:15 am | Break |
| 10:15– 10:30 am | Summary of SPERT Recommendation

Presenter: Amy Xia, M.D., Ph.D. (Executive Director, Biostatistics, Amgen) |
| 10:30 – 11:30 am | Open discussion of potential solutions |
| 11:30 – 11:45 am | Plans for follow-on activities by the biostatistics working group

Presenter: Janet Wittes, Ph.D. (President of Statistics Collaborative, Inc.) |
| 11:45 am – 12:00 pm | Closing remarks: Patrick Archdeacon |