Global Regulatory Landscape for Safety Monitoring: A Quantitative Perspective

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on behalf of the ASA Safety
Monitoring Working Group

ASA Safety Monitoring Working Group

- Established in 2015 by the ASA Biopharm Safety Statistics Working Group
- Goal
  - To empower the biostatistics community to play a more proactive role and better enable quantification in safety monitoring
- Key activities
  - Review safety regulation, survey industry, and interview thought leaders
  - Review statistical methodologies
- 2016 deliverables
  - June: DIA Annual
  - August: JSM Biopharm Section, DIA China Quantitative Science Forum
  - December: Deming Conference

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Stage 2: Cross-Disciplinary Scientific Engagement

- Goal
  - To empower the broader cross-disciplinary, cross-regional community to discover and promote practical quantitative solutions for safety monitoring during clinical development
- Key activities
  - Paper on global regulatory landscape and underlying quantitative principles
  - Best practice
    - Update program safety analysis plan (PSAP): cross-disciplinary planning document for safety, statistics, clinical, epidemiology, and regulatory
    - Cross-disciplinary framework for aggregate analysis and regulatory reporting
  - Methodology deep dive

BIOPHARMACEUTICAL SECTION

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Global Regulatory Landscape

CIOMS

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ICH

harmonisation for better health

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ICH Harmonization of Safety Monitoring

- Inherent risks for patients during drug development
  - All marketed drugs have associated risks
    - Investigational drugs have more uncertainty
  - Need proactive safety assessment
    - To enable effective risk management
- Three overlapping stages (same across all regions)
  - Premarketing safety monitoring
  - Safety specification at submission
  - Postmarketing pharmacovigilance (PV)

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Premarketing Safety Monitoring

ICH E2A Clinical Safety Data Management (October 1994)

- Serious and unexpected adverse drug reactions (ADRs) are subject to expedited reporting
  - Reasonable causal relationship judged by investigator and/or sponsor
  - Seriousness (not severity) guides reporting obligations
  - Unexpected: nature or severity is not consistent with source documents
- Clinically important increase in rate of expected serious ADRs is subject to expedited reporting
- Premarketing and postmarketing safety reporting concepts/practices are interdependent

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Safety Specification at Submission

ICH M4E(R2): The CTD — Efficacy (June 2016)

- Clinical overview should provide an evaluation of benefits and risks based on conclusions of relevant clinical studies
  - How findings support proposed dose and target indication
  - How prescribing information will optimize benefits and manage risks
- Summary of clinical safety should summarize safety in the intended patient population, integrating results of individual clinical study reports
  - Grouping studies and pooling results to improve precision of estimates and sensitivity to differences should generally be considered
  - Extensive safety analyses may be presented in a separate report and summarized here (for example, FDA Integrated Summary of Safety)
- Reports of efficacy and safety studies should include reports of all clinical studies (this where the ISS usually goes)

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Postmarketing Pharmacovigilance

ICH E2E Pharmacovigilance Planning (November 2004)

- PV planning activities for early postmarketing of a new drug
  - Improve benefit-risk balance by reducing risks
- Safety specification should be a summary of important identified risks, potential risks, and missing information
  - Should also address potentially at-risk populations and likely uses that have not been studied preapproval
- PV plan should include actions to address special concerns

CIOMS Is a Think Tank for Advancing International PV Practices

CIOMS WG	Descriptions	Resulting Regulatory Guidance
I	International Reporting of Adverse Drug Reactions (1990)	ICH E2A
II	International Reporting of Periodic Drug-Safety Update Summaries (1992)	ICH E2C
III	Guidelines for Preparing Core Clinical-Safety Information on Drugs (1999)	
IV	Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals (1998)	ICH E2C R2 (PBRER)
V	Current Challenges in Pharmacovigilance: Pragmatic Approaches (2001)	

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CIOMS Is a Think Tank for Advancing International PV Practices

- Divergence and disharmony on two recent reports
  - Natural part of healthy life-cycle management
    - Go beyond ICH technical requirements
- CIOMS VIII (2006): Signal Detection
  - Early adopter: EMA Good Pharmacovigilance Practices
  - Moving toward a new equilibrium at a higher level
    - FDA Sentinel system
    - Japan GVP and good postmarketing study practices
- CIOMS VI (2005): Management of Safety Information From Clinical Trials
  - Early adopter: FDA IND Safety Reporting Final Rule
  - Has not been adopted in other regions

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CIOMS Is a Think Tank for Advancing International PV Practices

CIOMS WG	Descriptions	Resulting Regulatory Guidance
VI	Management of Safety Information From Clinical Trials (2005)	IND Safety Reporting
VII	Development Safety Update Report (DSUR) (2006)	ICH E2F
VIII	CIOMS Working Group on Signal Detection (2006)	GVP Module IX
IX	Practical Approaches to Risk Minimisation for Medicinal Products (2010)	
X	Considerations for Applying Good Meta-Analysis Practices to Clinical Safety Data Within the Biopharmaceutical Regulatory Process (2016)	

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Management of Safety Information From Clinical Trials: Report of CIOMS Working Group VI

- One goal of CIOMS VI is to help bridge the gap between preapproval and postapproval activities to understand and manage risk
  - Mentioned in ICH E2A but not developed
- Also discusses the importance of having a systematic approach to managing risk during development
  - To ensure earliest possible identification of safety concerns
  - To take appropriate risk minimization steps
- A systematic, reproducible approach to detect, classify, and document adverse events (AEs) would enable investigators to develop clinical as well as statistical understanding of the safety profile

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Management of Safety Information From Clinical Trials: Report of CIOMS Working Group VI

- Safety monitoring during clinical development requires a partnership between clinical and statistical scientists
  - Requires thorough understanding of existing safety data, the patient population and relevant sub-populations, and risk factors for particular AEs
  - A meta-analytic review should be a routine part of the process so that ADRs, and differences in ADR rates, can be detected as readily as possible
- As the database increases, aggregate analysis becomes more important for detection and evaluation of signals
  - Mentioned in ICH E2A but not developed
  - Higher incidence for experimental compared control
  - Increased frequency of previously recognized SAR

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FDA Safety Guidance Documents That Go Beyond ICH Technical Requirements

- Format and Content of the Clinical and Statistical Sections of an Application (1988)
- Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2005)
- Premarketing Risk Assessment (2005)
- Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessments and Proposed REMS Modifications (2009)
- FDA IND Safety Reporting Final Rule (2010)
  - Safety Reporting Requirements for INDs (2012)
  - Safety Assessment for IND Safety Reporting (2015)
- Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Trials (2016)

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Safety Reporting Requirements for INDs: Guidance for Industry (December 2012)

- To improve the overall quality of safety reporting and to comply with requirements for IND safety reports based on data in the **aggregate**, "the sponsor should have in place a systematic approach for evaluating the accumulating safety data"
- "Reasonable possibility" for IND safety reporting
  A. "A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure"
  B. "One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug"
  C. "An **aggregate** analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group"

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Cross-Disciplinary Scientific Engagement

- The FDA IND Safety Reporting Final Rule highlights the importance of aggregate analyses for determining reasonable possibility of an association with study drug for serious adverse events (SAEs)
  - Safety physicians have been strong qualitative thinkers, focused on individual case review
  - The new guidance will require them to think more about quantitative methods, especially for disease-related events
  - Statisticians have a lot to offer in this area
  - Successful implementation will require collaboration between qualitative and quantitative thinkers

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Safety Assessment for IND Safety Reporting: Draft Guidance for Industry (December 2015)

- Sponsors should periodically review accumulating safety data
  - Integrated across multiple studies (completed and ongoing)
  - Provide a quantitative framework for measuring the evidence of an association (for unexpected events) or a clinically important increase (for expected events)
  - Make a judgment about "reasonable possibility" for IND safety reporting
- "It is critical for sponsors to detect and report, as early as possible, serious and unexpected suspected adverse reactions and clinically important increased rates of previously recognized serious adverse reactions"

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Cross-Disciplinary Scientific Engagement

- FDA is calling for
  - A multidisciplinary approach
  - Frameworks around aggregate review and level of evidence
    - Not statistical decision rules
  - Assessments that are product specific and decisions that are driven by medical judgment
- Opportunity to partner with FDA to champion safety issues
  - To protect human subjects participating in clinical trials
    - Terminate programs when unacceptable risks are discovered
  - To gain an understanding of the aggregate safety profile of drugs as early in their development as possible
    - Avoid premature termination of a program that shows promise even in the face of certain risks
    - Improve the way we identify patients at higher risk so that we can better position a medicine

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Quantitative Frameworks and Medical Judgment

- Statisticians can help multidisciplinary SMTs to think more quantitatively
  - By providing quantitative frameworks for medical judgment
  - Success will depend on dynamic, interactive, cross-disciplinary scientific engagement

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Backup Slides

Safety Assessment for IND Safety Reporting: Draft Guidance for Industry (December 2015)

- A safety assessment committee (SAC) and safety surveillance plan (SSP) are key elements
- FDA's preferred approach: SAC should regularly perform unblinded comparisons across treatment groups to detect numerical imbalances
  - Anticipated SAEs prespecified in the SSP (anticipated events)
  - Previously recognized SARs listed in the IB (expected events)
  - Appropriate steps should be taken to maintain overall study blinding
- Alternative approach: only perform unblinded comparison of event rates across treatment groups if the overall rate for all treatment groups of a specific SAE is substantially higher than a predicted rate
  - Sponsors should prespecify (in the SSP) predicted rates of anticipated events and expected events and guidelines for determining when an observed rate has exceeded the predicted rate

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Quantitative Framework: Bayesian Posterior Probabilities of Risk Elevation for AESI

Safety Monitoring Requires Flexibility

- Bayesian approach
  - Accommodates uncertainty
  - Natural for learning and decision making
  - Leverage prior information from earlier trials and related treatments
  - Unified framework for continuous safety monitoring using all of the available data
  - Probability statements that are easy to interpret
- Operating characteristics can be used to tune the probability threshold boundaries

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Quantitative Framework: Probability Threshold Boundaries

Probability (pooled rate > critical rate / data) ≥ probability threshold

- Parameters
  - Critical rate
  - Probability threshold
- Data
  - Overall number of events = x
  - Overall number of patients = n
  - Pooled rate = x/n

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Collaborative Process: Characterize Background Rates

Study incidence: not annualized (ADNI is 2 years, and other studies are 1.5 years)

Study	Description	N	Year	Age	Female	MMSE	Range	Syncope
Semagacestat	76-week phase 3 study (stopped early)	501	2008	73.2 (8.2)	53	20.8 (3.5)	16-26	1.4†
ADNI	2-year natural history, nontreatment study	190	2004	75.2 (7.5)	47.9	23.3 (2.0)	20-26	4.2‡
Bapineuzumab	18-month published trial	110	2005	67.9 (9.4)	59.8	20.7 (3.1)	16-26	1.8
Bapineuzumab	78-week phase 3 study	524	2007	71.9 (10.1)	50.3	21.2 (3.2)	16-26	2.5
Solanezumab	Two 18-month phase 3 studies	1025	2009	73.4 (7.9)	55.9	21 (3)	16-26	2.1

MMSE=Mini-Mental State Examination is used to test for complaints of problems with memory or other mental abilities, with higher scores indicating better cognitive function. †Stopped early; ‡2-year study of different patient population.

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Quantitative Framework: Probability Threshold Boundaries (continued)

Operating characteristics of probability threshold boundaries for syncope with a critical treatment rate of 3.0%

True Control Rate	True Treatment Rate	True Pooled Rate	Probability Threshold Boundary (percent of trials crossing the boundary)		
			70%	80%	90%
2.0%	2.0%	2.00%	9.6%	4.0%	0.9%
	3.0%	2.67%	63.7%	47.9%	26.8%
	4.0%	3.33%	98.9%	96.6%	91.7%
	5.0%	4.00%	100.0%	100.0%	100.0%
3.0%	2.0%	2.33%	30.1%	16.7%	5.8%
	3.0%	3.00%	90.6%	82.2%	64.3%
	4.0%	3.67%	100.0%	99.8%	99.0%
	5.0%	4.33%	100.0%	100.0%	100.0%

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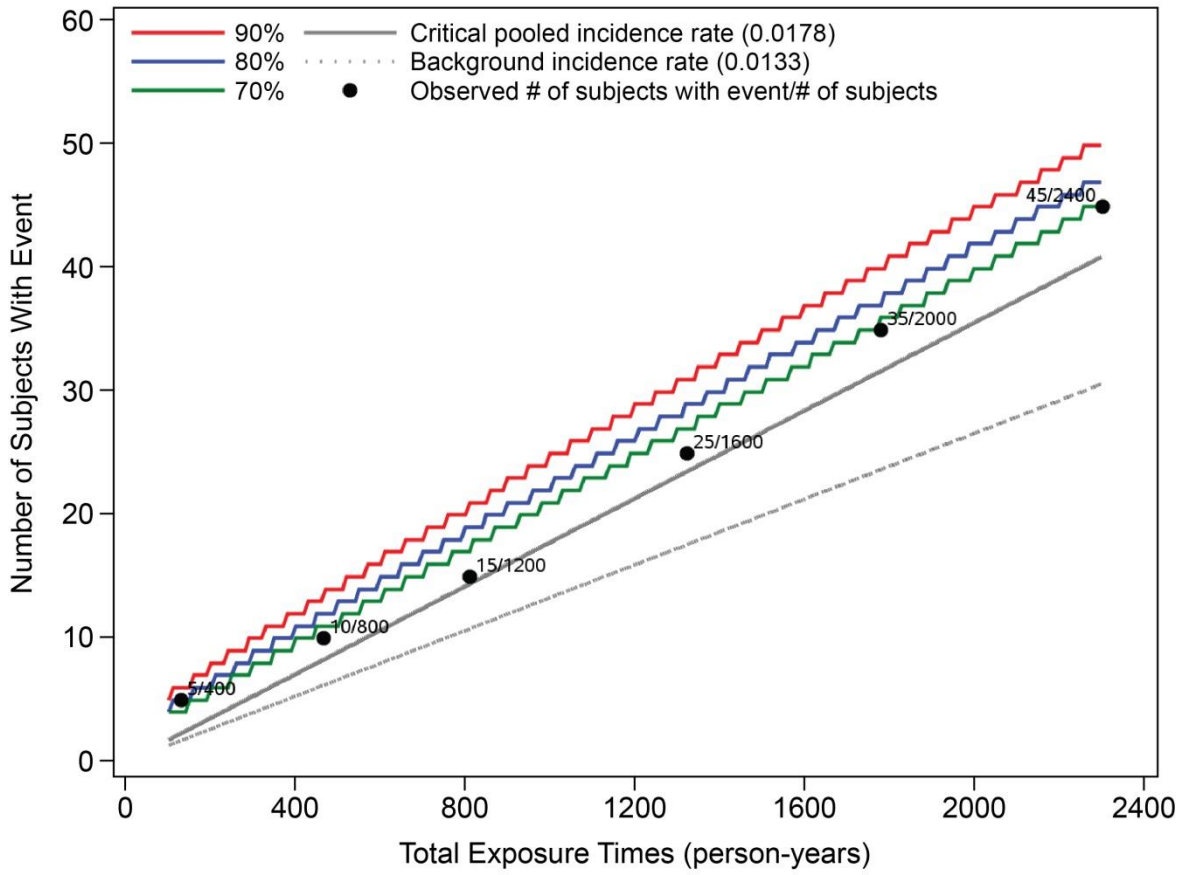
Quantitative Framework

Probability threshold boundaries for aggregate blinded safety monitoring: exposure-adjusted incidence rate (mock data)



Summary of Aggregate Safety Monitoring With Ongoing Blinded Studies

An alternative approach for anticipated events

- Collaborative process facilitates engagement with safety, clinical, epidemiology, and statistics
  - Characterize background event rates
  - Calibrate probability threshold boundaries
- Quantitative framework helps guide medical review and safety monitoring of the accumulating blinded data
  - General summary of aggregate safety profile
  - Bayesian posterior probabilities of risk elevation
- SMT uses medical judgment to decide on next actions
  - Have more events occurred than were expected?

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