ASA Biopharm's Safety Monitoring working group: Survey of statisticians, thought leaders and regulatory guidance

Greg Ball and William Wang, Merck

On behalf of the working group

Outline

1. Overview of the Safety Monitoring working group
2. Regulatory motivation
3. Interviews with industry thought leaders
4. Survey of statisticians and safety professionals

Overview

ASA Safety Monitoring Working Group

Established in 2015 by the ASA Biopharm section Safety Statistics WG

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

- August: JSM Biopharm Section, DIA China Quantitative Science Forum
- December: Deming Conference

Overview

Background

- What are the roles & opportunities for statisticians supporting safety monitoring?
- How do we collaborate effectively with safety physicians & scientists?
- Are we facing a gap between our current practices and new methods, tools and regulatory guidance?

Overview: Who We Are

WS1: Industry Practice Regulation

- Faiz Ahmad (Galderma)
- Greg Ball (Co-lead, Merck)
- Michael Colopy (UCB)
- Susan Duke (Co-lead, AbbVie)
- Robert (Mac) Gordon (Janssen)
- Qi Jiang (Amgen)
- Wenquan Wang (Morphotek)
- William Wang (Chair, Merck)

WS2: Methodology

- Michael Fries (Behring)
- Karolyn Kracht (Abbvie)
- Judy Li (Co-lead, FDA)
- Melvin Munsaka (Co-lead, Takeda)
- Matilde Sanchez (Arena)
- Krishan Singh (GSK)
- Ed Whalen (Pfizer)
- William Wang (Chair, Merck)
- Kefei Zhou (Amgen)

We are indebted to the 18 thought leaders who each spent at least an hour with us discussing their views on quantitative assessment of safety monitoring

Interviewed by Greg Ball, Susan Duke, Mac Gordon and Bill Wang

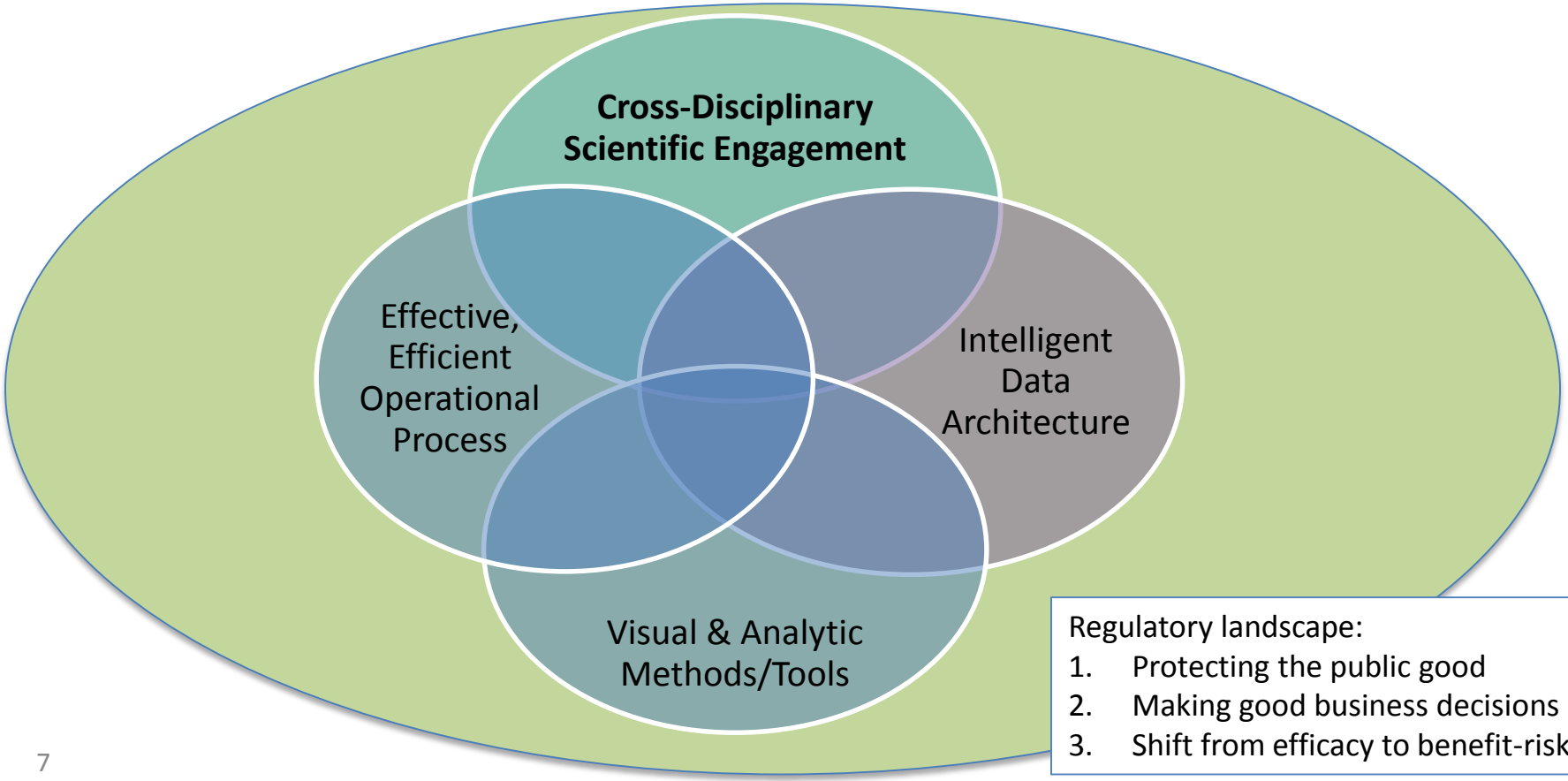
Safety Monitoring Statistical Advisors

Aloka Chakravarty (FDA)
Larry Gould (Merck)
Olga Marchenko (Quintiles)
Janet Wittes (Statistics Collaborative)
Brenda Crowe (Lilly)
Qi Jiang (Amgen)
Amy Xia (Amgen)

Thought Leaders

- Aloka Chakravarty (FDA)
- Bob Temple (FDA)
- Brenda Crowe (Lilly)
- Christy Chuang-Stein (Pfizer)
- Conny Berlin (Novartis)
- Dave DeMets (UW)
- Frank Rockhold (GSK, now Duke)
- Frank Shen (Abbvie)
- Janet Wittes (Statistics Collaborative)
- Jose Vega (Merck)
- Juergen Kuebler (CSL Behring)
- Lily Krasulja (Janssen)
- Mark Levenson (FDA)
- Mondira Bhattacharya (AbbVie)
- Olga Marchenko (Quintiles)
- Steve Snapinn (Amgen)
- Valerie Simmons (Eli Lilly)
- Walter Offen (Abbvie)

Overview: Four Pillars of Safety Statistics



Regulatory landscape:

1. Protecting the public good
2. Making good business decisions
3. Shift from efficacy to benefit-risk

Regulatory Motivation:

CIOMS Working Group on Safety

- Since 1986, CIOMS working groups on drug safety have been recognized as “think tanks” for advancing international pharmacovigilance practices

- The initiatives over the years have resulted in several major published reports
  - Many of these CIOMS recommendations have become part of regulatory guidance by ICH, EMA, FDA, etc

CIOMS: Council for International Organization of Medical Sciences

ICH: International Conference on Harmonization

EMA: European Medicines Association; FDA: Food and Drug Administration;

Regulatory Motivation:

10 CIOMS Working Groups on Safety

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)	

Regulatory Motivation:

10 CIOMS Working Groups on Safety

CIOMS WG	Descriptions	Resulting Regulatory Guidance
VI	Management of Safety Information from Clinical Trials (2005)	IND Reporting Rule
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 (In press)	

Regulatory Motivation:

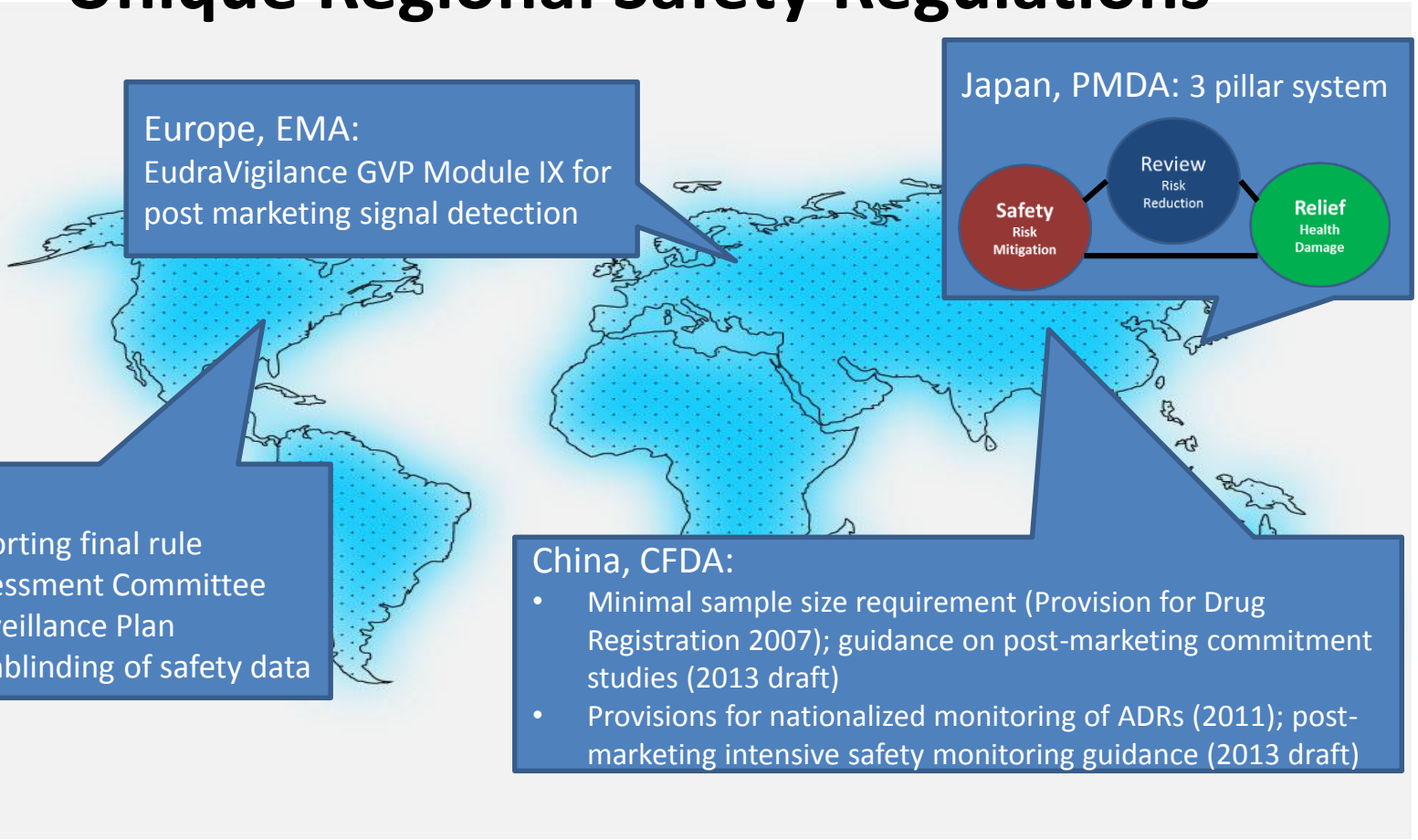
CIOMS VI: Close Linkage with Clinical Trial Safety

- Introduces proposals for enhancing the collection, analysis, evaluation, reporting and overall management of safety information from all safety data sources (special focus on **clinical trials)**

- A shift from the management of post-marketing safety information (spontaneous reports), to the management of clinical trial information

Regulatory Motivation:

Unique Regional Safety Regulations



Europe, EMA:
EudraVigilance GVP Module IX for post marketing signal detection

Japan, PMDA: 3 pillar system

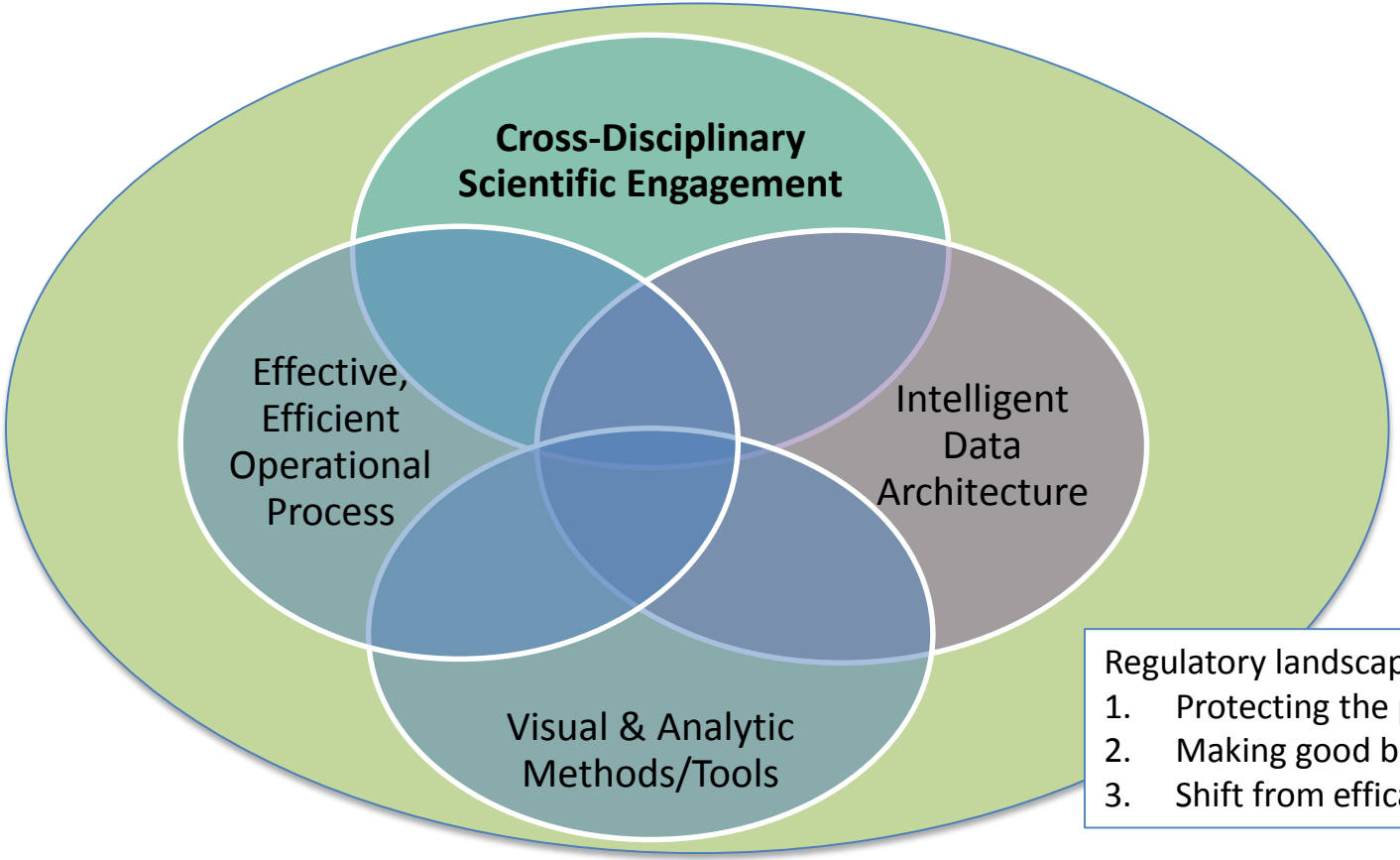
USA, FDA:
IND safety reporting final rule

- Safety Assessment Committee
- Safety Surveillance Plan
- Planned unblinding of safety data

China, CFDA:

- Minimal sample size requirement (Provision for Drug Registration 2007); guidance on post-marketing commitment studies (2013 draft)
- Provisions for nationalized monitoring of ADRs (2011); post-marketing intensive safety monitoring guidance (2013 draft)

Interviews: Four Pillars of Safety Statistics



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Thought Leader Interviews:

1. Cross-Disciplinary Scientific Engagement

- **"Safety is the new efficacy" -** a public health issue
  No longer just PV and spontaneous reports
  Requires experienced statisticians to interact with other departments

- **Safety Physicians need to rely heavily on quantitative expertise for aggregate data analysis and interpretation**

- **Siloed discussions of safety and benefit are not in the patients' best interest**

- **Statisticians need a safety mindset and need to closely engage other disciplines (eg safety physicians) to increase our impact**

- **Statisticians needs to understand about "why" before jumping into "how"**
  (Reference FDA Draft guidance on Safety Assessment Committees (SAC) - Dec 2015

Thought Leader Interviews

2. Effective, Efficient Operational Process

- ***The IND process is to protect patients, it's the way we do drug development***
  - SAC should not be too prescriptive
  - SAC should notify FDA early so they can own safety issues with sponsor

- **Lack of Resourcing is NOT a reason to NOT implement**
  - Embed SAC into existing process
  - Consider other ways to protect patients (eg IRBs and IDMCs)
  - Implementation can actually reduce burden on small organizations

- **Firewalls**

Controls to protect the trial's integrity and treatment blind

Thought Leader Interviews

2. Effective, Efficient Operational Process

- **Using a DMC as an SAC poses its own challenges**
  - DMCs typically work at the study level
  - External group creates challenges in ownership
  - SAC requires experience from more functional areas than DMC
  - How truly "independent" is an SAC when they must have intimate knowledge of the project?

- **Training**

Training for a different mindset - assessing the why before the how

- **Safety Statistics Support**

Dedicated group to develop sound approaches may become a necessity

Thought Leader Interviews

3. Visual & Analytic Methods/Tools

- **Regulatory landscape requires methods/tools to:**
  - Establish causality
  - Reduce volume of false safety signals
  - Mitigate risk / Identify subgroups

- **Trial integrity deserves more attention**
  - When, why, what value to public health?

- **Clinical judgment for decision making requires:**
  - Visual graphics & dashboards
  - Bayesian approaches

- **Benefit-risk assessment requires:**
  - Analyses throughout the drug development lifecycle
  - Patient perspectives

Thought Leader Interviews

4. Intelligent Data Architecture

- **Safety ecology**

  Utilize additional sources (eg RWE, animal studies, modeling, toxicology)
  Integrate disparate sources of data
  Controlled access & firewalls to maintain trial integrity

- **Quality via standardization and proactive collection**

  Leads to more effective safety assessment & communication
  - CDISC, SDTM, ADaM, analysis templates, standard processes

  Methods for monitoring data quality are important

Industry Survey

Statisticians & Safety Professionals

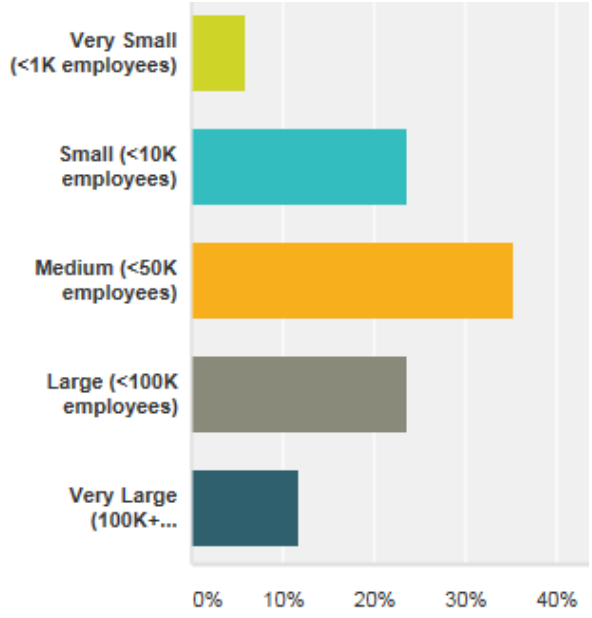
- **Requested participation from 35 companies of all sizes**
- **1 survey per company** (no company names collected)
- **Goals:**
  - Assess levels of involvement statisticians have in a wide range of quantitative safety analyses
  - Assess alignment of operational processes with regulatory guidance
  - Assess various types of new & traditional approaches being used today
  - Assess areas where statisticians want & need training

Industry Survey

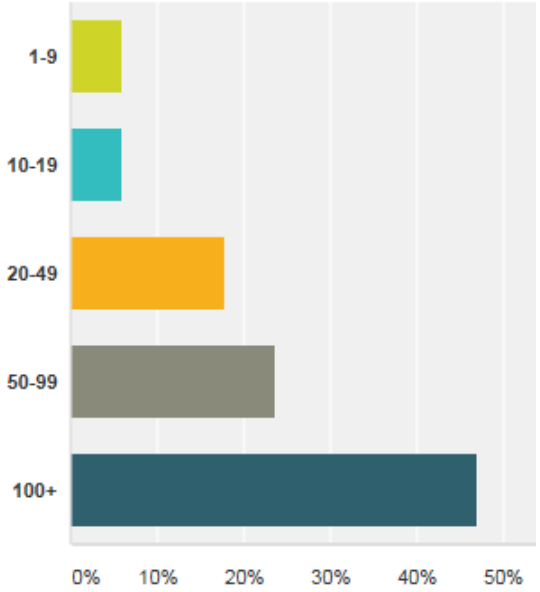
Statisticians & Safety Professionals

Response rate: 50% (holding out for 100%)

Size of Company



Number of Statisticians



Conclusions

- **The evolving safety regulatory landscape demands quantitative enablement**

  Goal: ***to empower the biostatistics community to play a more proactive role and better enable quantification in safety monitoring***

- **Thought leader advice focused on 4 pillars in safety statistics**
  1. Culture embraces safety mentality
  2. Process enables a proactive multidisciplinary approach
  3. Methods/tools allow scientific answers to the right questions
  4. Data quality and data integration serve as infrastructure foundation
- **Stage I focused on review and survey**
  - **Stage II will focus on empowerment**

    Best quantitative practice, enhanced safety methods/tools, cross-disciplinary outreach