Key Sources of Uncertainty in the Assessment of Benefits and Risks of Pharmaceuticals and Associated Challenges

Institute of Medicine Workshop: Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products
February 12–13, 2014, US FDA Campus, White Oak, MD

Tarek A. Hammad, MD, PhD, MSc, MS, FISPE

Executive Director, Epidemiology, Merck
Former Deputy Director of Epidemiology, CDER, FDA

www.DrTarekHammad.com

Disclaimer

- The views expressed in this talk are mine, and as such, the principles, ideas, and perspectives provided here do not necessarily reflect those of my employer

2

The Roadmap…

1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle
3. Going back to the basics: Key sources of uncertainty
4. Considerations for the optimal approach to address uncertainty around BR assessment

22:57

3

The Roadmap…

1

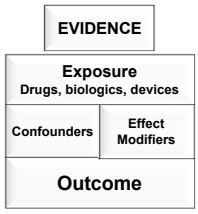
- **<u>What we are dealing with:</u> Decision dimensions in drug development (context)**

22:57

4

Decision Dimensions in Drug Development…

Hammad et al, 2013 "The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective". *Clinical Pharmacology and Therapeutics*. doi:10.1038/clpt.2013.118.

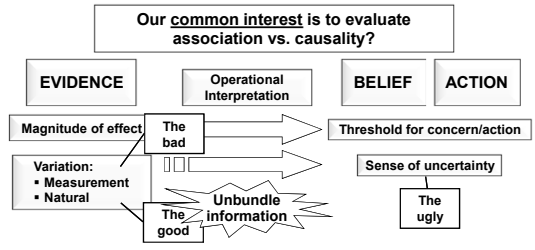


General structure adopted from Richard Royall's book, "Statistical Evidence: A Likelihood Paradigm". Cited from Larry Magder notes "Statistical Analysis of Epidemiologic Data", 2001.

5

Decision Dimensions in Drug Development…

Hammad et al, 2013 "The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective". *Clinical Pharmacology and Therapeutics*. doi:10.1038/clpt.2013.118.

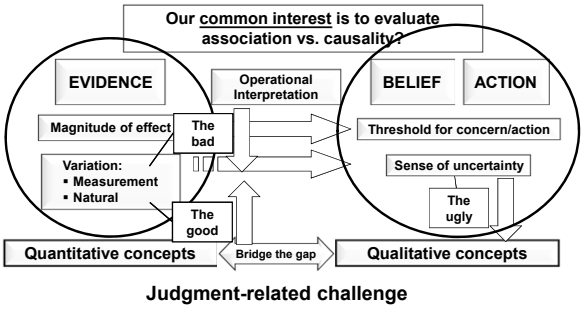


General structure adopted from Richard Royall's book, "Statistical Evidence: A Likelihood Paradigm". Cited from Larry Magder notes "Statistical Analysis of Epidemiologic Data", 2001.

6

Decision Dimensions in Drug Development…

Hammad et al, 2013 "The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective". *Clinical Pharmacology and Therapeutics*. doi:10.1038/clpt.2013.118.



Judgment-related challenge

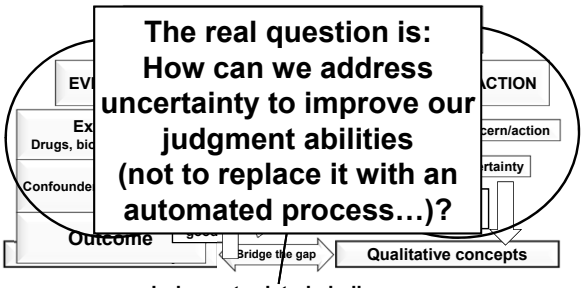
General structure adopted from Richard Royall's book, "Statistical Evidence: A Likelihood Paradigm". Cited from Larry Magder notes "Statistical Analysis of Epidemiologic Data", 2001.

7

Decision Dimensions in Drug Development…

Hammad et al, 2013 "The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective". *Clinical Pharmacology and Therapeutics*. doi:10.1038/clpt.2013.118.

The real question is: How can we address uncertainty to improve our judgment abilities (not to replace it with an automated process…)?



Judgment-related challenge

General structure adopted from Richard Royall's book, "Statistical Evidence: A Likelihood Paradigm". Cited from Larry Magder notes "Statistical Analysis of Epidemiologic Data", 2001.

8

Are all drugs' benefit created equal?

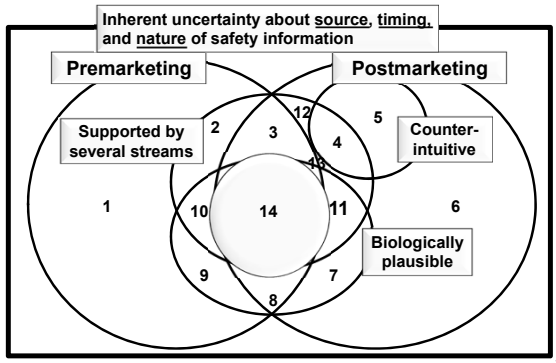
Well, perhaps not…

How about risk?

Are all adverse events created equal?

Domains of Adverse Events in Drug Development:

Not All AEs Are Created with Equal Uncertainty…!



22:57 11

In a Nutshell…

- **What we are dealing with:**
  - **A complex decision-making process that has inherent quantitative and qualitative dimensions, reflecting the interaction between multiple streams of evidence with many stakeholders**
  - **Drugs with benefits and risks that are not created equal**
    - **Context matters significantly in the evaluation process – the same set of facts might lead to a different course of action!**

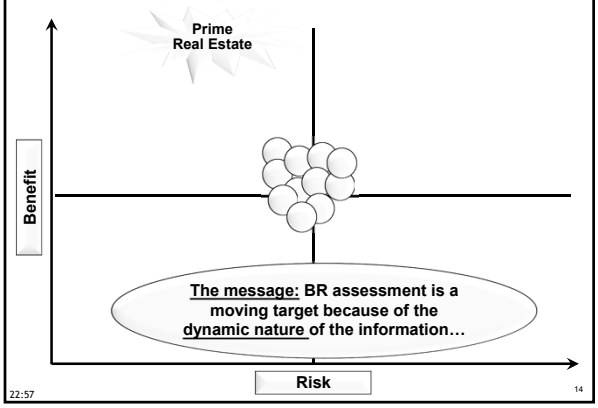
22:57 12

The Roadmap…

1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle

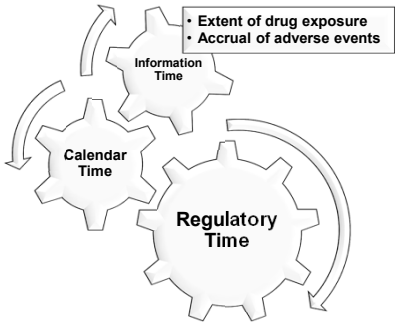
22:57 13

Which Drugs Might NOT Need BR Assessment?



22:57 14

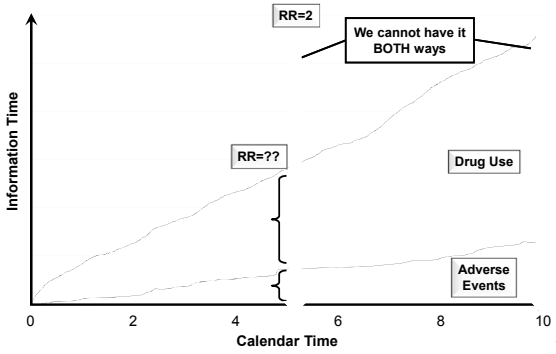
However, Regulatory Time Is the Product of the Information and the Calendar Times



Judith C. Maro and Jeffrey S. Brown. Impact of exposure accrual on sequential postmarket evaluations: a simulation study. *Pharmacoepidemiology and Drug Safety* 2011; 20: 1184–1191

15

Regulatory Time Is the Product of the Information and the Calendar Times



16

nature publishing group STATE OF THE ART

Received 14 May 2013; accepted 29 May 2013; advance online publication 10 July 2013. doi:10.1038/clpt.2013.118

The Future of Population-Based Postmarket Drug Risk Assessment: A Regulator's Perspective

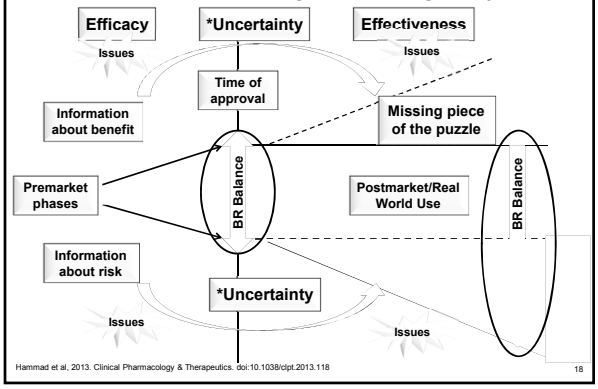
TA Hammad[1], GA Neyarapally[2], S Iyasu[3], JA Staffa[4] and G Dal Pan[2]

The US Food and Drug Administration emphasizes the role of regulatory science in the fulfillment of its mission to promote and protect public health and foster innovation. With respect to the evaluation of drug effects in the real world, regulatory science plays an important role in drug risk assessment and management. This article discusses opportunities and challenges with population-based drug risk assessment as well as related regulatory science knowledge gaps in the following areas: (i) population-based data sources and methods to evaluate drug safety issues; (ii) evidence-based thresholds to account for uncertainty in postmarket data; (iii) approaches to optimize the integration and interpretation of evidence from different sources; and (iv) approaches to evaluate the real-world impact of regulatory decisions. Regulators should continue the ongoing dialogue with multiple stakeholders to strengthen regulatory safety science and address these and other critical knowledge gaps.

22:57

17

Current Realities Regarding the Population-based Benefit-risk Assessment Throughout the Drug Lifecycle



Hammad et al, 2013. Clinical Pharmacology & Therapeutics. doi:10.1038/clpt.2013.118

18

In a Nutshell…

- We are talking about:
  - A dynamic benefit-risk assessment process in which we superimpose group experience on individual patients
  - An imbalance in the sources, timing, and nature of information on benefit and risk in the pre- and post-marketing periods

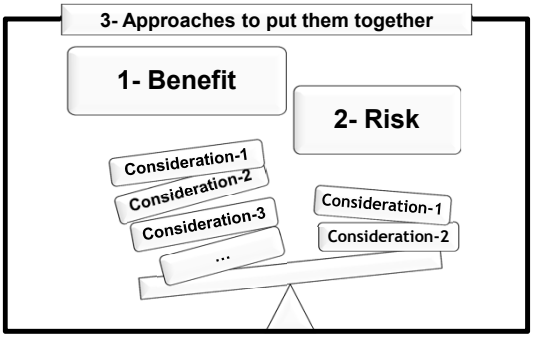
22:57 19

The Roadmap…

1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle
3. Going back to the basics: Key sources of uncertainty

22:57 20

The Three Domains of BR Assessment: Almost Three Different Fields of Science…

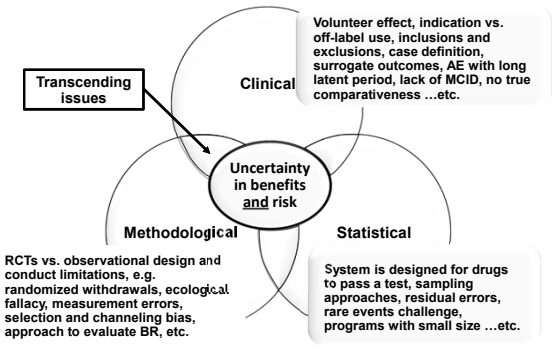


22:57 21

Breaking it down to the basic elements…

To make it more manageable…

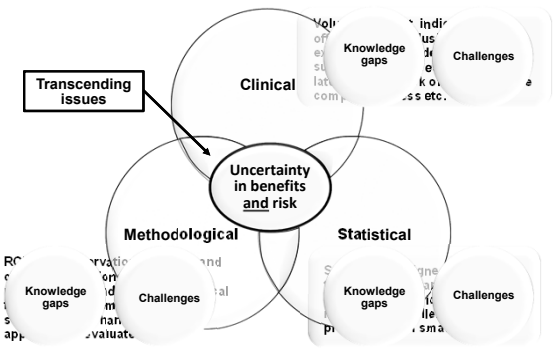
Challenges and knowledge gaps, underlying uncertainties in BR assessment, have three unique, yet intertwined sources…



Classification adopted from Berlin et al. Clinical Trials 2012; 10: 20 –31

23

Challenges and knowledge gaps, underlying uncertainties in BR assessment, have three unique, yet intertwined sources…



Classification adopted from Berlin et al. Clinical Trials 2012; 10: 20 –31

24

Uncertainties in BR assessment, have three unique, yet intertwined sources…

Operational aspects: The "Fourth" Dimension

1. Need more info: can not coerce patients to participate post-market
2. Benefit: system not designed to quantify it, no MICD
3. Risk: lack of "threshold of risk tolerance" (regulators vs. payers vs. healthcare providers vs. patients)
4. Surveillance effort:
   - "Time trend bias" related to the dynamic nature of all the pieces
   - Unknown impact of regulatory actions on BR balance
   - Impact of "Confounding by Information" on BR balance
   - "Volume" bias due to large number of small negative studies
   - Need for true EHR/big data infrastructure
5. …

The Roadmap…

1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle
3. What the debate is all about: Scientific thought process and the core debates in BR
4. Considerations for the optimal approach to address uncertainty around BR assessment

26

What is the "Status Quo"?

The "Precautionary Principle"…

- **A strategy to cope with possible risks in which scientific understanding is incomplete…**
  - **"A need to err on the side of caution because of uncertainties about the safety of technologies or infrastructure"**
  - **"When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm"**
  - **"Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent [environmental] degradation"**

Hans-Georg Eichler, Brigitte Bloechl-Daum, Daniel Brasseur, Alasdair Breckenridge, Hubert Leufkens, June Raine, Tomas Salmonson, Christian K. Schneider, Guido Rasi. "The risks of risk aversion in drug regulation". *Nature Reviews Drug Discovery* 12(907–916), 2013. DOI:doi:10.1038/nrd4129

What is at stake?

Nature Reviews Drug Discovery | AOP, published online 15 November 2013; doi:10.1038/nrd4129

PERSPECTIVES

OPINION

The risks of risk aversion in drug regulation

Hans-Georg Eichler, Brigitte Bloechl-Daum, Daniel Brasseur, Alasdair Breckenridge, Hubert Leufkens, June Raine, Tomas Salmonson, Christian K. Schneider and Guido Rasi

Abstract | Drugs are approved by regulatory agencies on the basis of their assessment of whether the available evidence indicates that the benefits of the drug outweigh its risks. In recent years, regulatory agencies have been criticized both for being overly tolerant of risks or being excessively risk-averse, which reflects the challenge in determining an appropriate balance between benefit and risk with the limited data that is typically available before drug approval. The negative consequences of regulatory tolerance in allowing drugs onto the market that turn out to be unsafe are obvious, but the potential for adverse effects on public health owing to the absence of new drugs because of regulatory risk-aversion is less apparent. Here, we discuss the consequences of regulatory risk-aversion for public health and suggest what might be done to best align acceptance of risk and uncertainty by regulators with the interests of public health.

What About the Patient Perspective: How Does It Relate to Uncertainty?

- In practice, the "Precautionary Principle" might conflate uncertainty about the extent of the risk with the uncertainty about the willingness of patients to accept the risk
- Patient perspective is likely to change over time depending on stage of life and disease severity, adding to the uncertainty
- Group experience vs. individual decisions

22:57 31

In Short, the Optimal Approach to Address Uncertainty in BR Assessment Should Take Into Consideration...

- The complexity of the decision-making process: quantitative and qualitative dimensions, not all drugs created equal, context matters, sources of uncertainties (clinical, methodological, and statistical), operational challenges
- The dynamic nature of the BR assessment with clear imbalance in the sources, timing, and nature of information on benefit and risk
- The goal of addressing uncertainty is to improve our judgment, not to replace it with an automatic process…
- Identify and address knowledge gaps to achieve quick wins, while minding the scientific boundaries of our tools
- The need for a better way to truly characterize and incorporate pertinent patient prospective

22:57 32