Challenges to the Regulator in Communicating Uncertainties in Risks of Approved Pharmaceuticals

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- *"To be approved for marketing, a drug must be safe and effective for its intended use."*

  -PDUFA V Draft Implementation Plan (Feb 2013)

Premise: A determination has been made based on review of scientific evidence that the benefits of the product outweigh the risks when used according to the label.

Scientific Evidence

- How is scientific evidence defined?
- Not all scientific evidence is created equal
- Not everyone will conclude the same thing of the same scientific evidence

Scientific Evidence – how do we define it?

- Section 505(d) of FDCA defines *substantial evidence* as:

  "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof"
- Applies to the determination of a drug's effectiveness. There is no legal standard defining substantial evidence for determination of safety.

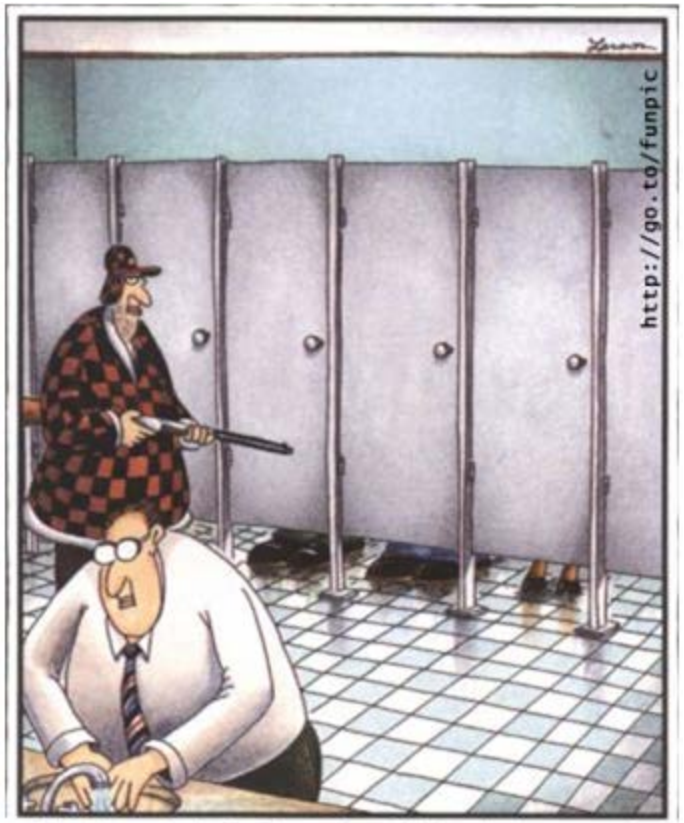
Not all Evidence is Created Equal

Level	Type of scientific evidence
Ia	Scientific evidence obtained from meta-analyses of randomized clinical trials.
Ib	Scientific evidence obtained from at least one randomized clinical trial
IIa	Scientific evidence obtained from at least one well-designed, non-randomized controlled prospective study
IIb	Scientific evidence obtained from at least one well-designed, quasi-experimental study
III	Scientific evidence obtained from well-designed observational studies, such as comparative studies, correlation study or case-control studies.
IV	Scientific evidence obtained from documents or opinions of experts committees and/or clinical experiences of renowned opinion leaders.

Scientific Evidence for Safety Determination

- Pre-clinical
- Safety studies (tQT, mechanistic)
- Randomized, controlled clinical trials
- Spontaneous reporting of post-marketing adverse events
- Case reports/case series
- Epidemiologic studies

Same evidence examined ≠ Same conclusion reached



His rifle poised, Gus burst through the door, stopped, and listened. Nothing but the gentle sound of running water and the rustling of magazines could be heard. The trail, apparently, had been false.

My viewpoint is based on synthesizing all the available data, recognizing that each individual piece of data has its strengths and limitations. Ideally, results of a well-designed, rigorously executed, and carefully analyzed clinical trial designed to answer the question at hand would be available. This is not the case here. Nonetheless, based on the totality of the evidence and the consistency of the signal across data sources, I simply can not conclude, for public health and regulatory purposes, that the observed findings are not real.

Because I have concluded that the benefits of [redacted] do not outweigh its risks, I continue to support market withdrawal as an appropriate regulatory action. This

The [redacted] case is an example of the reality that the science (specifically the data) rarely is so definitive that it points to an obvious and widely agreed upon regulatory decision. In the absence of definitive data FDA must still make sound decisions. These are necessarily based on the available data and our understanding of its strengths and weaknesses, but must also consider the law, regulations, precedents for similar cases, the disease treated by the drug, alternative treatment options, patient and physician preferences, "population" benefit-to-risk considerations and even the role of the practice of medicine versus government decision-making and the importance of autonomy of physicians and patients to make decisions about medicines. In the end, all the decisions we make at FDA become a judgment of whether the benefits of the drug outweigh the risks when used as labeled, and these judgments are very much influenced by how one considers all the complex factors that must be considered and weighed.

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prescribers and patients. Given that I find the available data on a differential risk between [redacted] to be inconclusive, I believe that it is important to retain both drugs as choices in patients who are felt to need [redacted]s. I believe that prescribers and patients can make, and have been making, informed decisions in the absence of a restrictive REMS and recommend the labeling changes outlined above instead of a burdensome new REMS.

In conclusion, I believe that there are clinical data suggestive of [redacted] risks associated with [redacted]. However, the sources of data from which this signal arises have serious limitations upon which a regulatory decision for drug withdrawal should not be based. Despite this, the data suggesting increased [redacted] risk can still be communicated to prescribers and patients to allow informed medical decisions and prescribing practices for [redacted], including the decision to never use [redacted] or to select [redacted] only after failing other [redacted] therapies. Some might ask why I don't just recommend the drug's withdrawal given that the safety signal is sufficient enough to justify its relegation to second-line or even last-option therapy. After all, withdrawal would effectively eliminate any chances for the drug to continue to do harm. While I cannot dispute that fact, I believe withdrawal of [redacted] in the setting of scientific uncertainty is an inappropriate display of FDA's authority to make a decision for all healthcare providers because of concern that these trained professionals can not reasonably decide on or take responsibility for the use of this drug. I am also concerned that such an action would set an unsettling precedent for future regulatory decisions or may be referenced in legal challenges to the FDA to withdraw other drugs based on meta-analyses and observational studies of similar uncertainty for drug risk.

Approaches to Inform Risk Communication

- Internal procedures
  - FDA review template
  - Briefings (Intra/interoffice, regulatory, Center Director)
  - Committees (REMS oversight, Safety First Steering Committee)
- External procedures
  - Drug Safety Oversight Board (federal partners)
  - Advisory Committee Meetings (external scientific experts)
  - Published perspectives
  - Outreach (medical community, patients)

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment