FoREMS & More

Reviewing a "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making"

May 8, 2013
Today’s Session

Reviewing a "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making”

Speaker:
– Jeff Fetterman – President, ParagonRx
Today’s Session

Reviewing a "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making"

This webinar will:

- Review the Draft Implementation Plan
- Identify key insights for risk management professionals
- Comment on how this fits in the overall evolution of benefit-risk management trends
Today’s Session

Reviewing a "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making”

Submitting Questions:

- Click on ParagonRx Host under the users tab and click on Private Chat to initiate the chat feature

Resize slides:

- Click “Fit to Screen”
- Ability to zoom in and out
Structured Approach to Benefit Risk Assessment in Drug Regulatory Decision-Making

May 8, 2013
Although the meaning of “safe” is not explicitly defined in the statutes or regulations that govern approval, and recognizing that all drugs have some ability to cause adverse effects, the safety of a drug is assessed by determining whether its benefits outweigh its risks.

FDA’s [PDUFA V] commitments include the publication of a draft five-year plan that describes the Agency’s approach to further develop and implement structured benefit-risk assessment in the human drug and biological product review process. This document fulfills the PDUFA V commitment to publish the draft plan.
Drug Regulatory Decision-Making…

… at the intersection of Law, Science, Medicine, Policy, and Judgment

- FD&C Act and the Public Health Service Act
- Guidances
- Scientific method
  - Well established for benefit
  - Drug safety more challenging
- Social and behavioral science
- Judgment based on training and experience

"A framework for benefit-risk decision-making can greatly inform and clarify the regulatory discussion"
Framework Development Considerations

- Within legal, regulatory and policy limits
- Throughout lifecycle of drug
- Facilitate identification of critical issues
- Focus discussions on the weighing of those issues
- Integrate into existing process of review teams
- Qualitative descriptive approach supported by quantification
Framework Development Approach

- Retrospective study
- Interviews
- Basic Structure
- Pilot Project
## Structure of a Benefit-Risk Framework (BR-Framework)

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tbody>
<tr>
<td><strong>Analysis of Condition</strong></td>
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**Benefit-Risk Summary Assessment**
### Structure of a Benefit-Risk Framework (BR-Framework)

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<th>Evidence and Analysis of Condition and Current Treatment Options</th>
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<tbody>
<tr>
<td><strong>Analysis of Condition</strong></td>
<td>▪ Summary and assessment of the severity of the condition that the product is intended to treat and other therapies available to treat the condition</td>
</tr>
<tr>
<td><strong>Current Treatment Options</strong></td>
<td>▪ Represents:</td>
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<td></td>
<td>▪ Context of the decision that can provide useful information for weighing the benefits and risks of the drug under review</td>
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<td>▪ <strong>Therapeutic area</strong> considerations of the framework—These considerations are distinct from the other drug-specific considerations in the framework</td>
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**Benefit and Risk**

- Summary and assessment of submitted evidence concerning the drug under review
- Key considerations of benefit:
  - Results of clinical trials
  - Clinical meaning of primary and secondary endpoints
  - Appropriate analyses of subpopulations
- Key considerations of risk:
  - Adequacy of safety database
  - Severity and reversibility of AEs
  - Potential for sub-optimal management in the post-market setting of potential concern
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**Risk Management**

- Summary and assessment of any efforts that could help mitigate the identified safety concerns
- Ensure that the drug is directed to those patients for whom the risk is considered acceptable

Benefit-Risk Summary Assessment
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<td><strong>Two considerations inform regulatory decisions</strong></td>
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<td>Current Treatment Options</td>
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<tr>
<td>Benefit</td>
<td>- Identifying facts, uncertainties, and assumptions that need to be made to address what is not known</td>
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<td>Risk</td>
<td>- Presents:</td>
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<td></td>
<td>- Facts</td>
<td></td>
</tr>
<tr>
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<td>- Uncertainties</td>
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<td>Risk Management</td>
<td>- Assumptions made to address these uncertainties that contribute to the assessment of benefit and risk</td>
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**Two considerations inform regulatory decisions**

#### 2. Conclusions and Reasons

- Conclusions that must be made about each decision factor
  - Subjective interpretation of the evidence for each aspect of the benefit-risk assessment
- Captures the implications of:
  - Facts
  - Uncertainties
- Assumptions with respect to:
  - Regulatory decision making
  - Drawing conclusions from the evidence and uncertainties
  - Explaining the bases for those conclusions
Summary Assessment

**Benefit-Risk Summary Assessment**

- Succinct well-reasoned summary clearly explaining the FDAs rationale for the regulatory action including important clinical judgments that contributed to the decision
  - Summary should integrate:
    - Analyses of benefit and risk and;
    - Applicable statutory and regulatory standards into a coherent explanation of the conclusions reached
  - Assessment draws on:
    - Key supporting evidence and uncertainties
    - Accounts for the understanding of the condition

- Considerations:
  - Available therapies that establish the context in which benefits and risks are weighed
  - Rationale to support the labeling and other risk management
  - Post-marketing requirements/commitments if necessary to further characterize the benefits and/or risks of the drug
  - Differences of opinion within review team are noted in the assessment along with an explanation of how they were resolved or taken into account in the final decision
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**Benefit-Risk Summary Assessment**

“A single framework provides a standardized, predictable, and accessible form that communicates the basis for FDAs regulatory decision to the public, while also documenting the decision for reference as FDA considers similar benefit-risk assessments in the future”
Recap Overview of BR-Framework Structure

Decision Factors

- Analysis of Condition
- Current Treatment Options
- Benefit
- Risk
- Risk Management

Evidence and Uncertainties

- Facts
- Uncertainties
- Assumptions made to address uncertainties contributing to the assessment of benefit and risk

Conclusions and Reasons

- Conclusions made regarding each decision factor
- Subjective interpretation of evidence for each aspect of BR-assessment
- Captures the implications of facts, uncertainties, and assumptions

Benefit-Risk Summary Assessment

Succinct well-reasoned summary clearly explaining FDAs rationale for the regulatory action including important clinical judgments that contributed to the decision
STEP 1. Primary clinical reviewer creates draft of benefit-risk assessment framework

STEP 2. Draft framework further refined by the Cross-Discipline Team Leader (CDTL) in CDERS 21st Century Review process to incorporate input from other disciplines

STEP 3. Benefit-risk framework reviewed and finalized by the signatory authority as part of the review of the action package

STEP 4. With expanded implementation of the framework in PDUFA V, additional experience may suggest modifications to this potential implementation strategy
Benefit-Risk Framework Implementation in PDUFA V
Benefit-Risk Framework Implementation in PDUFA V
Further Development FY 2013

PDUFA V commitments include reference to revision of, **CDER Clinical Review Template**, Office and Division Director **Summary Memoranda Templates**, and CBER documents to incorporate structured benefit-risk assessment in the human drug review process (**CBER Clinical Review Template**).

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**Continuous**

**CDER Clinical Review Template**

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**Summary Memoranda Template**

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**CBER Clinical Review Template**

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**Improvements**

Goal is to produce a user-friendly template for review staff and generates work products that are valuable and informative to CDER and CBER leadership.
Key Considerations in the Post-Market Setting

- New info on benefit and risk is identified in PM setting
- Direct link between BR-framework and PDUFA V commitment to draft guidance on whether REMS is necessary
- BR-framework will inform regulatory decision-making, including whether REMS is necessary
- Use of framework facilitates balanced consideration of benefits and risks of drug
Characterization of Uncertainties in Benefits and Risks

“Although drug regulatory decisions are informed by an extensive body of evidence on safety and efficacy of a product, FDA must draw conclusions from imperfect data” (e.g., absence of info, conflicting findings, marginal results)

Two Areas of Focus in FY 2013

1. Characterizing the uncertainty in how well the BR-assessment (based on pre-market clinical trial data) translates to the post-market setting after drug is approved and used in a wider patient population

2. Implementing systematic approach that specifies:
   • Sources and strengths of each piece of evidence
   • Conclusions drawn, explaining how uncertainty weighed on the decision which can lead to a more explicit communication of regulatory decisions because level of uncertainty about a result or finding that becomes available in post-market setting
Staged Implementation
FY 2014-2017

“FDA plans to use a staged approach in implementing the benefit-risk framework in human drug review in order to allow opportunity for continued refinement of framework and its integration before further expansion into additional types of applications”

<table>
<thead>
<tr>
<th>Application Group</th>
<th>Fiscal Year</th>
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<tbody>
<tr>
<td>New Molecular Entity New Drug Applications</td>
<td>2014-2015</td>
</tr>
<tr>
<td>Original Biologics License Applications</td>
<td></td>
</tr>
<tr>
<td>Efficacy Supplements for New/Expanded Indications</td>
<td>2016</td>
</tr>
<tr>
<td>All Original NDAs</td>
<td>2017</td>
</tr>
</tbody>
</table>
Additional PDUFA V Commitments on Enhancing Benefit-Risk Assessment
# BR Public Workshops in PDUFA V

FDA commits to holding 2 public workshops on BR considerations from regulator’s perspective

<table>
<thead>
<tr>
<th>1st Workshop</th>
<th>2nd Workshop</th>
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<tbody>
<tr>
<td>Targeted early FY 2014</td>
<td>Targeted date TBD</td>
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<tr>
<td>Focus on various frameworks and methods available, including their appropriate application to drug regulatory decision-making</td>
<td>Focus on results of implementing frameworks at regulatory agencies in pre-market application review and post-market safety review</td>
</tr>
<tr>
<td>Anticipates participation of other drug regulatory authorities also implementing frameworks in their drug decision process</td>
<td>– Share challenges and lessons learned in applying structured approach to regulatory decision-making</td>
</tr>
<tr>
<td>Examine ability of various frameworks to make explicit:</td>
<td>– Further detail regarding FDAs plan to be updated as implementation progresses in PDUFA V for this workshop will be included in an update</td>
</tr>
<tr>
<td>– Benefit &amp; risk considerations and associated uncertainties</td>
<td></td>
</tr>
<tr>
<td>– assumptions that are part of drug regulatory decision-making</td>
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Evaluation of the BR-Framework

- Draft five-year plan to evaluate the impact of the BR-framework

- Specifics of implementation approach are still evolving with experience and feedback received by reviewers on implementation of the framework
  - Integration of framework concepts into clinical review template during FY 2013 will lead to best practices, which will be applied to implementation of the framework in FY 2014

- Evaluation questions expected to be examined are, “Whether the framework provides…”:
  1. A clearer explanation of FDA approval decisions to public stakeholders (e.g., patients, consumers, HCPs, and industry)
  2. Value to internal reviewer communications and discussions related to pre-market regulatory decisions
  3. Value in supporting considerations of emerging safety and efficacy information in post-market drug decision contexts

“Expected evaluation will begin in FY 2015-2016 after full implementation has occurred in a sufficient number of application reviews”
Early 2013 FDA anticipates publishing set of disease areas that will be addressed during the first three years of PDUFA V

Patient-Focused Drug Development

FDA recognizes the unique and valuable perspective of patient considerations

Belief that drug development review process could benefit from a more **systematic** and **expansive** approach to obtaining the patient perspective

FDA commitment to new initiative with the objective of obtaining patient perspective on available therapies for set disease areas during FY 2013-2017

Similar process will be conducted for determining the list of disease areas for FY 2016-2017

For each disease area, FDA will conduct a public meeting and invite participation from FDA review divisions, relevant patient advocacy community, and other interested stakeholders

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QUESTIONS?

Click on ParagonRx Host and select Private Chat to access the chat dialogue box
TERM and Lehigh University Department of Industrial Systems Engineering present the TERM Summit

REMS Assessments: An Advanced Concepts Seminar Among Stakeholders

Hyatt Regency Bethesda
Thursday, May 23, 2013
7:30 am – 4:30 pm
The First Annual TERM Summit

REMS Assessments: An Advanced Concepts Seminar Among Stakeholders

Confirmed Topics & Speakers include:

- **Assessing REMS Program Impact: Historical Approaches, Current Catalysts for Improvement and Future Considerations**
  - Gary Slatko, MD, MBA - Director, Office of Medication Error Prevention and Risk Management, FDA
  - Mary Willy, PhD - Associate Director, Division of Risk Management, FDA
  - Terry Toigo, RPH - Associate Director, Drug Safety Operations, Center for Drug Evaluation

- **Emerging Recommendations for Evaluating the Effectiveness of Risk Minimization Activities: Highlights of CIOMS IX Working Group and EMA’s GVP Module XVI (as available)**
  - Meredith Smith, PhD, MPA - Senior Scientific Director, Risk Management, Global & Research Development, AbbVie
The First Annual TERM Summit

REMS Assessments: An Advanced Concepts Seminar Among Stakeholders

- Evaluating REMS and Behavioral Change Strategies from an Implementation Science Perspective
  - Russell Glasgow, PhD - Deputy Director, Implementation Science, Division of Cancer Control and Population Sciences, National Cancer Institute, NIH

- Case Study: A Brief History and Current Plan of Action for Measuring the Performance of Long-acting Opioid Risk Minimization
  - Paul Coplan, MS, DSc, MBA - Executive Director Risk Management & Epidemiology, Purdue Pharma

- Quantifying REMS Program Burden on the Healthcare System Using Simulation Modeling
  - Robert H. Storer, PhD - Co-Director of the Integrated Business and Engineering Honors Program, Lehigh University
  - M. Kris Srinivasan, MD, MBA, MHSE - Clinical Consulting Director, ParagonRx International
  - Marc Deluca, MHSE candidate - Client Services Manager, ParagonRx International
The First Annual TERM Summit

REMS Assessments: An Advanced Concepts Seminar Among Stakeholders

- **Conjoint Analysis of Physician Preferences as a Measure of Burden**
  - Christene Song - Director, Quantitative Market Research, Campbell Alliance

- **Using Novel Data Sources to Assess the Patient Perspective on REMS Burden**
  - David Blaser, PharmD - Health Data and Drug Information Clinical Specialist, PatientsLikeMe
  - Meredith Smith, PhD, MPA - Senior Scientific Director, Risk Management, Global & Research Development, AbbVie

- **Health Literacy Measures of Patient Burden**
  - Michael Wolf, PhD, MPH - Associate Professor of Medicine and Learning Sciences and Associate Division Chief for General Internal Medicine, Northwestern University
The First Annual TERM Summit

**REMS Assessments: An Advanced Concepts Seminar Among Stakeholders**

- **TERM** (Trends Emerging in Risk Management), established in 2011, is a group of pharmaceutical safety, risk management, and academic healthcare professionals who meet periodically for problem solving, advanced mutual learning, and experience sharing. Three regional working groups established in New York, Chicago, and San Francisco have identified initiatives to advance the discipline of risk management. This summit is one such initiative.

- The **TERM Summit** is a one-day working seminar in which advanced concepts for assessing the outcomes of health interventions will be presented. The objective is to understand the current state of the science and define a research plan to close gaps.
The First Annual TERM Summit

REMS Assessments: An Advanced Concepts Seminar Among Stakeholders

- For inquiries regarding the TERM Summit:
  - Visit, www.termcommunity.com
    - Click on the “Contact us” tab to submit any questions or comments
    - To view more information regarding agenda, speakers, topics, and venue, click on “Meetings & Events” tab
QUESTIONS?

Click on ParagonRx Host and select Private Chat to access the chat dialogue box
FoREMS & More

- Occurs the second Wednesday of every month
- 12:00 pm ET
- Next session:
  - Wednesday, June 12, 2013
Future FoREMS & More

- We encourage you to submit any future topics you’d like us to cover
- Do you want to be a speaker for a future FoREMS & More?
- Contact us:
  - Jeff Fetterman
  - jfetterman@paragonrx.com
  - 888.459.8080

THANK YOU!