The Practical Application of Regulatory Science

Impact on Regulatory Policy and Practice

Lawrence Liberti, PhD, RAC, RPh
Executive Director
Presentation objectives

• Identify some key activities of regulatory science that can impact key stakeholders
• Provide examples of the practical application of these activities
• Offer observations around implementing these activities
What is Regulatory Science?

The science of developing and validating new standards and tools to

• evaluate and assess the benefit/risk of medicinal products,

• facilitating sound and transparent regulatory decision making.

• Through analysis of regulatory frameworks...advance knowledge of these systems in general

CBG-MEB definition, Regulatory Science Network Netherlands Newsletter
Examples we can learn from

- evaluating and assessing the benefit/risk of medicinal products,
- facilitating sound and transparent regulatory decision making.
- Through analysis of regulatory frameworks...advancing knowledge of these systems in general
Key Benefit-Risk Initiatives

US FDA's Approach to Benefit/Risk Assessment

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Unmet Medical Need</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Risk</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
</tbody>
</table>

CIRS Seven Step Framework for Benefit/Risk Assessment

1. Decision context
2. Develop a value tree of Benefits Risks
3. Provide rationale for inclusion of Benefits & Risks
4. Valuing/scoring of Options
5. Weighting Benefit & Risk Parameter
6. Visual Presentation
7. Expert Judgement

Six Steps used in the BRAT Framework which was transferred to CIRS in December 2011

1. Define the decision context
2. Identify and select benefit and risk outcomes
3. Identify and extract source data
4. Customize the Framework
5. Assess outcome importance
6. Display and interpret key benefit-risk measures

The EMA Approach: PrOACT-URL Model

Table 2. The eight-step PrOACT-URL model applied to benefit-risk assessment of medicinal products

- Define drug, dose, formulation, indication, population, comparator(s), time horizon for outcomes, and perspective of the decision makers (regulator, sponsor, patient, physician, or payer)
- Select all important outcomes
- Create initial Value Tree
- Define preliminary set of measures for each outcome
- Document rationale for outcomes to be included in/excluded from the initial Value Tree
- Determine and document all data sources (e.g., clinical trials, observational studies)
- Populate data source table with relevant data
- Include detailed references and annotations to support subsequent interpretations
- Create summary measures and input into master Summary Table
- Modify the Value Tree based on further review of the data and clinical expertise
- Refine the outcomes and measures
- May include turning outcomes considered to be not relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group
- Summarize data into tabular and graphical displays to aid interpretation
- Review summary measures and source data, and identify and fill information gaps
- Interpret summary information
- Conduct sensitivity analyses to assess the impact of uncertainty in data sources on displays or summary measures
1. Decision context

2. Develop a value tree of benefits and risks

3. Provide rationale for benefits and risks

4. Relative importance of benefits and risks

5. Valuing or scoring of options

6. Evaluation of uncertainty

7. Visual presentation

8. Expert judgement and communication
Mapping the Principles of Key Initiatives to the UMBRA Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Framing the Decision</th>
<th>Identifying Benefits and Risk</th>
<th>Assessing Benefits and Risks</th>
<th>Interpretation and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framework</td>
<td>Step 1: Decision Context</td>
<td>Step 2: Building the Value Tree</td>
<td>Step 3: Refining the Value Tree</td>
</tr>
<tr>
<td></td>
<td>Step 7: Concise presentation of Results (Visualisation)</td>
<td>Step 8: Final Recommendation-Expert Judgment and Communication</td>
<td></td>
</tr>
</tbody>
</table>

**FDA**
- Analysis of conditions
- Unmet medical need
- Clinical Benefits & Risks
- Evidence and uncertainties
- Words: Telling the Story
- Conclusions and Rationale Risk Management Plans

**EMA**
- Nature & Framing of the Problem
- Objectives; Favourable & Unfavourable Effects
- Options to be evaluated & the Conseq.
- Trade offs Benefit/Risk Balance
- Evaluating Uncertainty
- Effects Table Risk tolerance
- Consistency of Decisions (Linked Decisions)

**CIRS iSABRE**
- Decision Context
- Building the Value Tree
- Rationale for Benefits & Risks in overall BR
- Weighting of Benefits & Risks
- Valuing or Scoring of Options
- Visualisation
- Expert Judgement & Risk Management

**CIRSBRAH**
- Define Decision Context
- Identify Outcomes: Build Value Tree
- Customise framework: Refine Value Tree
- Assess relative importance of different outcomes: Weighting or Ranking Other Stakeholders
- Evaluating Uncertainty?
- Display & Interpret Key BR metrics
- Validate Results
- Decision & communication of BR Assessment
CIRS-BRAT: Bringing Consistency to the Dynamic Assessment of BRs of Medicines

- Over 340 unique downloads
- 178 unique organisations
- From 41 countries
- Industry, regulators, HTA, academia, consultants

http://www.cirs-brat.org/download/
international Summary Approach to Benefit-Risk Evaluation (iSABRE): Bringing international consistency to BR documentation

- Piloted by: Malaysia, Indonesia, China, Philippines, Chinese Taipei, ANVISA
- Interest from: JordanFDA, SAPRHA/MCC
- Proposed to: Singapore, Thailand, Vietnam
Examples we can learn from

• evaluating and assessing the benefit/risk of medicinal products

• facilitating sound and transparent regulatory decision making

• Through analysis of regulatory frameworks...advancing knowledge of these systems in general
• “An organization that seeks to improve its decisions should also routinely measure the quality of its decision-making”

Thinking Fast and Slow (Kahneman, 2011)
Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives†

Ronan Donelan¹, Stuart Walker² and Sam Salek³*

¹Global Regulatory Affairs, Quintiles, Dublin, Ireland
²Centre for Innovation in Regulatory Science, London, UK
³Department of Pharmacy, University of Hertfordshire, Hatfield and Institute for Medicines Development, Cardiff, UK

ABSTRACT

Purpose Currently, there is no qualified understanding of the influences, behaviours and other factors that impact the decision-making of individuals and organisations involved in the development of new medicines. The aim of this qualitative study was to investigate and identify the important issues that influence quality decision-making.

Methods Semi-structured interviews were carried out with 29 senior decision-makers from the pharmaceutical industry and regulatory authorities. The study participants were invited to discuss and review their perception of decision-making within their organisation, its role in drug development and the regulatory review and their awareness and use of decision-making techniques and the impact and monitoring of decisions.

Results The analyses (using NVivo 8® software) resulted in the identification of 32 major and 97 sub-themes that were consolidated into 19 overarching themes. These included items such as quality and validity of data, time considerations, organisational and cultural influences, analytical and logical approach, qualification and experience, subjective and personal considerations, policy influences, precedents for similar previous decisions, understanding of the decision in question, impact analyses, audit trail, education and awareness, individual versus corporate decision-making and frameworks. Relationships between themes were identified. The 19 overarching decision-making themes were integrated into a framework for quality decision-making.

Conclusion This study has achieved its aim of exploring decision-making from the perspective of the individual and the organisation working in drug development and the regulatory review and has identified issues and considerations relating to making good quality decisions and allowed for the generation of a framework to aid quality decision-making.

KEY WORDS—qualitative; interviews; decision-making; quality; regulatory agencies; pharmaceutical industry; individual; organisation; framework; pharmacoepidemiology
Agency and company QoDoS Organisational responses mapped to the 10 Quality Decision Making Practices

1. Have a structured, systematic approach
2. Assign clear roles and responsibilities
3. Assign values and relative importance to decision criteria
4. Evaluate internal and external influences/biases
5. Examine alternatives
6. Consider uncertainty
7. Re-evaluate with new information
8. Perform impact analysis of decision
9. Ensure transparency and provide record trail
10. Effectively communicate decision basis

- Company average
- Agency average
Examples we can learn from

- evaluating and assessing the benefit/risk of medicinal products,
- facilitating sound and transparent regulatory decision making.
- Through analysis of regulatory frameworks...advancing knowledge of these systems in general
An Ideal Medicine Regulatory Pathway

Pre-submission meeting
- Clarity on requirements / check lists
- Authority / Industry workshops

Submission
- Priority / accelerated review
- Risk-based review
- Specialized review by product/country
- Predictability – structured process & timelines

Scientific Assessment/Review process
- Consistent Clinical/Technical review approach
- Convergence on international standards
- Better collaboration across agencies

Approval

Post-approval
- Consistent Post-approval commitments and monitoring

Source: CIRS Workshop, Lima, Peru 2014
Primary Facilitated Regulatory Pathways (FRPs)

• Primary FRP (Expedited Regulatory Pathways): Pathways that speed the development, review and approval of a product; typically implemented by a SRA* for a first non-dependent review

Accelerated approval/Assessment, Priority review, Breakthrough therapy, CM authorisation, MA under Exceptional Circumstances, Sakigake, etc.

• Secondary Used by NRAs or regional regulatory initiatives (RRIs) wherein their decisions can be expedited by the reliance on or recognition of prior reviews.

Verification or Abridged reviews, “Pro-forma” registration, WHO PQP/Collaborative Registration process, etc

*([https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf](https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf)).

Alternative terms: e.g. Well-resourced authority, Strong Regulatory Authority; Mature Regulatory Authority, Competent Regulatory Authority
NAS median approval time by review type  2011-2015- (Primary FRPs)

*‘Expedited review’ refers to EMA ‘Accelerated Assessment’ and FDA/PMDA/Health Canada/Swissmedic ‘Priority Review’.

**The EMA approval time includes the EU Commission time.

***TGA does not currently have an expedited evaluation programme.

© CIRS, R&D Briefing 59

CIRS R&D Briefing 59. May 2016
FDA FRPs: Speeding access; stimulating innovation

FDA Facilitated Regulatory Pathways: Visualizing Their Characteristics, Development, and Authorization Timelines
Secondary FRPS: Reliance and Recognition

- **Primary FRP**: Pathways that speed the development, review and approval of a product; typically implemented by a SRA* for a first non-dependent review

- **Accelerated approval/Assessment, Priority review, Breakthrough therapy, CM authorisation, MA under Exceptional Circumstances, Sakigake**

- **Secondary (Reliance Pathways) Used by NRAs or regional regulatory initiatives (RRIs) wherein their decisions can be expedited by the reliance on or recognition of prior reviews-based on RISK STRATIFICATION**
### Step 4: Types of risk-stratified reviews that could be implemented by agencies based on their capabilities

<table>
<thead>
<tr>
<th>Class</th>
<th>Full (Standard)</th>
<th>Full (expedited)</th>
<th>Secondary FRPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1. Prepared to Implement FRPs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (Mature)</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>B (Maturing)</td>
<td>YES</td>
<td>POSSIBLY</td>
<td>YES</td>
</tr>
<tr>
<td>Tier 2: Have the capacity to implement some FRPs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (Realising)</td>
<td>POSSIBLY</td>
<td>POSSIBLY</td>
<td>YES</td>
</tr>
<tr>
<td>D (Evolving)</td>
<td>NA</td>
<td>NA</td>
<td>YES</td>
</tr>
<tr>
<td>E (Foundational)</td>
<td>NA</td>
<td>NA</td>
<td>POSSIBLY</td>
</tr>
<tr>
<td>Tier 3: Do not have the capacity to benefit from an FRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (Ill-Equipped)*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Regional Regulatory Initiatives**

| Regional Regulatory Initiatives | POSSIBLY | POSSIBLY | YES | YES |

*Pro-Forma Registration*

Liberti L: A proposed framework for a globally applicable pragmatic approach to using facilitated regularity pathways (FRPs) Thesis. Utrecht University, 2017
Can Risk-Stratification Improve Efficiency?

Time (days)

- Verification Median
- Abridged median
- Full route
## Regulatory Science Support Risk-Based Frameworks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Regulatory Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feedback to industry on submitted dossiers</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Details of technical staff to contact</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Pre-submission scientific advice to industry</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Official guidelines to assist industry</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Industry can track progress of applications</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Summary of the grounds on which approval was granted</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Approval times</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Advisory committee meeting dates</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
<tr>
<td>Approval of products</td>
<td>Saudi Arabia (5/9), Australia (9/9), Canada (8/9), Singapore (6/9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authority</th>
<th>Canada (3/5)</th>
<th>Singapore (4/5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval of products</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Approval times</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Advisory committee meeting dates</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Industry can track progress of applications</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Summary of the grounds on which approval was granted</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Official guidelines to assist industry</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Pre-submission scientific advice to industry</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Details of technical staff to contact</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Feedback to industry on submitted dossiers</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

1. Licensing Department, Saudi Food and Drug Authority, North Ring Road, Al Nafal Unit (1), Riyadh 13132-6238, Saudi Arabia
2. Saudi Food and Drug Authority, North Ring Road, Al Nafal Unit (1), Riyadh 13132-6238, Saudi Arabia
3. Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
4. Global Development Programme, Center for Innovation in Regulatory Science, 77 Hatton Garden, London EC1N 8JF, UK
5. Center for Innovation in Regulatory Science, 77 Hatton Garden, London EC1N 8JF, UK
6. School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, Wales
A Proposed Integrated Framework for the use of Primary and Secondary FRPs

Liberti L: A proposed framework for a globally applicable pragmatic approach to using facilitated regularity pathways (FRPs) Thesis. Utrecht University, 2017
Presentation objectives: Recap

Identify some key activities of regulatory science that can impact key stakeholders

- Benefit-risk assessment
- Decision making
- FRPs

Provide examples of the practical application of these activities

- BR frameworks and their global applicability
- QoDOS as a systematic approach to assessing DM
- Mapping FRPs and assessing their impact on regulatory review times

Offer observations around implementing these activities

- Fit-for-purpose approaches to BR assessments and communication
- Ease of assessing DM via QoDOS
- Practical recommendations for best practices/use of primary and secondary FRPs
The Practical Application of Regulatory Science

Impact on Regulatory Policy and Practice

Lawrence Liberti, PhD, RAC, RPh
Executive Director