Regulatory Perspectives on Benefit-Risk Assessment

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UNIVERSITY OF SOUTHERN CALIFORNIA
OVERVIEW

- The regulatory review process
- Expectations and challenges
- The Consortium – an example of collaboration and innovation
- More challenges
- The way ahead
OVERVIEW OF REGULATORY PROCESSES FOR A NEW DRUG APPLICATION

Submission → Evaluation → Market Authorisation (or maybe not) → Post-market variations and pharmacovigilance
OVERVIEW OF REGULATORY PROCESSES FOR A NEW DRUG APPLICATION

- Clinical Evaluation
- Non-clinical Evaluation
- Quality Evaluation

- Decision on benefit-risk balance

- Regulatory Decision – Market approval and post-market commitments

Benefit-risk assessment

- Evaluator’s recommendation
- Peer review
- Expert opinions/Consultations
- Medical/Scientific Advisory
- Dialogues with applicants
EXPECTATIONS ON REGULATORY AUTHORITIES

The Stakeholders

Within agency
- Applicant/Industry
- HTAs/Payors

The regulatory authority

Healthcare professionals
Other agencies
Patients/Consumers
## EXPECTATIONS ON REGULATORY AUTHORITIES

### Stakeholders

<table>
<thead>
<tr>
<th>Category</th>
<th>Questions</th>
</tr>
</thead>
</table>
| **Within agency**      | • Why and how did we make that decision?  
                          • Have we been consistent?                                                                                                                                 |
| **Applicant/ Industry**| • Why and how did they make that decision?  
                          • Why is it different from what is expected?                                                                                                                                 |
| **HTAs/ Payors**       | • What is the evidence for use?  
                          • Is the use and reimbursement justifiable?                                                                                                                                 |
EXPECTATIONS ON REGULATORY AUTHORITIES

Stakeholders

Healthcare professionals
• What is the evidence for use?
• How do I use it?
• What should I look out for?

Patients/ Consumers
• Is this effective and safe?
• How would this help me?
• Is this really for me?
• Why is it not available?

Other agencies
• Why and how did they make that decision?
• How does it differ from our decision?

The regulators as an effective surrogate for the consumers
EXPECTATIONS ON REGULATORY AUTHORITIES

The Stakeholders

Within agency
Applicant/ Industry
HTAs/ Payors

Healthcare professionals
Other agencies
Patients/ Consumers

• Quality decision and accountability
• Effective communication
Evolving Expectations...

- Benefit-risk balance
- Moving away from separate contribution of efficacy evidence and risk data
- The balance will change along the life cycle of the product

Is everything equal? Or are some more important?
EVLING EXPECTATIONS...

- Alignment to the rapidly advancing medical sciences; towards benefit-risk balance
- Timely access to quality, safe and efficacious drugs
- Accountability to stakeholders
  - Clear and consistent basis of decision
  - Transparency of decision making process
  - Effective communication of decisions to stakeholders
  - Governance and audit of the processes
- Product life cycle management
...AND ENDLESS CHALLENGES

- Resource limitations
- Regulations are governed by the law, not so for medical sciences
- Obligation to scientific evidence, yet required to meet social demands
- Wide scope of expectations
- Increasing vocal stakeholders
- Harmonising requirements in the background of changing standards
COLLABORATION

• Formation of Consortium
• Setting common goals
• Seeking external help

INNOVATION

• A universal benefit-risk assessment framework
• A benefit-risk assessment template
THE CONSORTIUM

Consortium on Benefit-Risk Assessment (established 2009) - COBRA

- Therapeutic Goods Administration (TGA), Australia
- Health Canada, Canada
- SwissMedic, Switzerland
- Health Sciences Authority (HSA), Singapore

- Four similar-sized agencies sought the assistance of Centre for Innovation in Regulatory Sciences (CIRS) for a standardised systematic approach - work-sharing and joint reviews
- Piloted the use of the benefit-risk template based on the universal framework for the assessment of medicines
NEED FOR ENHANCEMENT

• Current frameworks are general in nature
  • From submission to post-market
  • From evaluation to regulatory decisions
  • Supported by policies, standard operating procedures, training…
• The framework specific for evaluation remains more or less the same throughout these years
  • An identified area for enhancement
  • Potential tool to aid in fulfilling the evolving expectations from stakeholders on regulatory authorities
• Need to discuss benefit-risk balance rather than the separate contribution of efficacy and safety
BARRIERS TO IMPLEMENTING A FRAMEWORK

- Lack of a framework recognised or accepted by stakeholders
- Lack of a scientifically validated framework

**REQUIREMENTS OF A FRAMEWORK**

<table>
<thead>
<tr>
<th>Utility and Scope of a universal framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Need for a universal benefit-risk assessment framework</td>
</tr>
<tr>
<td>• Importance of a universal benefit-risk framework developed for registration purposes</td>
</tr>
<tr>
<td>• Importance of a universal benefit-risk framework applied throughout life cycle of a medicine</td>
</tr>
<tr>
<td>• Applicability of a universal benefit-risk framework to health technology assessment agencies</td>
</tr>
<tr>
<td>• Utility of a universal benefit-risk assessment framework</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purposes of a universal framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Application of a universal benefit-risk framework to benefit-risk management plans</td>
</tr>
<tr>
<td>• Transparency and consistency of decision-making</td>
</tr>
<tr>
<td>• Communication of decision</td>
</tr>
</tbody>
</table>
MANY FRAMEWORKS....

US FDA 5-step BR framework

EMA PrOACT-URL

MCDA

CIRS 7-step framework

Nova Nordisk BRAIN

PhRMA BRAT framework
## COMPARING THE FRAMEWORKS

<table>
<thead>
<tr>
<th>Frameworks reviewed</th>
<th>Core elements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frameworks reviewed</strong></td>
<td><strong>Core elements</strong></td>
</tr>
<tr>
<td>Framing the decision</td>
<td>Identifying benefits and risks</td>
</tr>
<tr>
<td>Analysis of conditions and unmet medical needs</td>
<td>Clinical benefits, risks</td>
</tr>
<tr>
<td>Nature and framing of the problem</td>
<td>Objectives, favourable and unfavourable effects</td>
</tr>
<tr>
<td>Define decision context</td>
<td>Identify outcomes, extract source data: build value tree</td>
</tr>
<tr>
<td>Decision context</td>
<td>Disease profile</td>
</tr>
<tr>
<td>Building the value tree for all benefits and risks</td>
<td>Rational for which benefits and risks to be included for benefit-risk assessment</td>
</tr>
<tr>
<td>Decision context</td>
<td>Building the value tree</td>
</tr>
</tbody>
</table>

### US FDA
- **Analysis of conditions and unmet medical needs**
  - Clinical benefits, risks
  - Evidence and uncertainties
- **Conclusions and reasons, risk management plans**

### EMA PrOACT-URL
- **Nature and framing of the problem**
- **Objectives, favourable and unfavourable effects**
- **Alternatives regarding options to be evaluated and the consequences**
- **Trade-offs and benefit-risk balance**
- **Evaluating uncertainty**
- **Effects table and risk tolerance**
- **Consistency of decisions (linked decisions)**

### PhRMA BRAT framework
- **Define decision context**
- **Identify outcomes, extract source data: build value tree**
- **Customise framework: refine value tree**
- **Assess relative importance of different outcomes: weighting or ranking, other stakeholders**
- **Evaluating uncertainty**

### Novo Nordisk BRAIN
- **Decision context**
- **Disease profile**
- **Weighting**
- **Scoring**
- **Evidence evaluation**
- **Weighted scores**
- **Presentation**
- **Overall conclusion**

### CIRS 7-step framework
- **Decision context**
- **Building the value tree for all benefits and risks**
- **Rational for which benefits and risks to be included for benefit-risk assessment**
- **Weighting of benefits and risks**
- **Valuing or scoring of options**
- **Evaluating uncertainties**
- **Visualisation**
- **Expert judgment and risk management**

### Universal benefit-risk framework
- **Decision context**
- **Building the value tree**
- **Customising the value tree**
- **Weighting of benefits and risks**
- **Scoring the options**
- **Evaluating uncertainties**
- **Concise presentation of results (visualisation)**
- **Expert judgment**
DEVELOPMENT OF A NEW FRAMEWORK

Universal Methodologies for Benefit-Risk Assessment

The UMBRA Eight Step Benefit Risk Framework

- Overarching framework (UMBRA) providing underlying principles for the process of making a quality decision
- Supported by the Benefit-risk Assessment Template and User Manual
DEVELOPMENT OF A NEW FRAMEWORK

Universal Methodologies for Benefit-Risk Assessment

- Framing the decision
  1. Decision context

- Identifying benefits and risks
  2. Building the value tree
  3. Refining the value tree

- Assessing benefits and risks
  4. Relative importance of benefits and risks
  5. Evaluating the options

- Interpretation and recommendations
  6. Evaluating uncertainty
  7. Concise presentation of results (visualisation)

- 8. Expert judgment and communication
ACTIVITIES OF THE CONSORTIUM

• Pilot functionality study on paper-based BR assessment template
• Retrospective feasibility study on a electronic version
• Prospective feasibility study on the revised assessment template
• The UMBRA and the BR Template supports the current approach used by the four agencies
• A tool for documentation, showing the progressive logic and basis of decision

• Based on EMA Reflection Paper on benefit-risk assessment methods

• Correlates to and supports the UMBRA framework

• User Manual
A tool for documentation, showing the progressive logic and basis of decision

Based on EMA Reflection Paper on benefit-risk assessment methods

Correlates to and supports the UMBRA framework
USER MANUAL

- Consists of glossary for terms used in the template and clarifications on how to complete the template.
PRACTICAL USE OF THE BR TEMPLATE

Preparing and understanding the context of the request and the scope for which the evaluation will be confined to

- Provides a focus on matters that would actually affect the decision
- Provides an initial qualification of the medical need for this request

UMBRA framework Step 1

SECTION 1. Background
The aim of this proforma is to provide the means whereby the key benefits and risks, together with the uncertainties (strengths of evidence and limitations of data) that drive the benefit-risk assessment can be documented systematically in the light of the available evidence and therapeutic indication in accordance with the CHMP Assessment Template. This section contains a mixture of factual key data and interpretation through value judgments.

1.1 Specify the proposed therapeutic indication

1.2 Treatment modalities evaluated in this submission

1.3 Other currently available treatment options NOT considered or evaluated

1.4 What are the known risks with compounds of the same therapeutic class?

1.5 Is this product for an unmet medical need?

1.6 Aims of treatment and expected effect size? i.e., define if there are established minimally significant clinical benefits in the light of both internal and publicly available guidelines.
## PRACTICAL USE OF THE BR TEMPLATE

- Incorporating relevant **contributions from other aspects of evaluation** besides clinical assessment of benefits and risks

### 2.1 Quality Overall Summary

<table>
<thead>
<tr>
<th>This prefills summary 8.1.2 and proforma section 7.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please tick the box if there are no relevant findings in the quality assessment that will contribute significantly to the clinical assessment of benefits and risks.</td>
</tr>
<tr>
<td>Please provide comments in the box below if there are relevant findings in the quality of the product that may affect significantly the clinical assessment of benefits and risks.</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
</tbody>
</table>

### 2.2 Non-Clinical Overall Summary

<table>
<thead>
<tr>
<th>This prefills summary 8.1.3 and proforma section 7.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please tick the box if there are no relevant findings in the non-clinical assessment that will contribute significantly to the clinical assessment of benefits and risks.</td>
</tr>
<tr>
<td>If there are relevant findings, please complete the comments section.</td>
</tr>
</tbody>
</table>

### 2.3.1 Human Pharmacology: Overall Summary

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc.
PRACTICAL USE OF THE BR TEMPLATE

- Clearly **articulating the benefits and risks** as identified by evaluator AND the company

**UMBRA framework Steps 2 & 3**

### SECTION 3. Identified Benefits and Risks

**3.1 List all the BENEFITS as documented** *(This prefills summary 8.3.1)*

<table>
<thead>
<tr>
<th>List all benefits of treatment for this indication as inferred in the submission</th>
<th>Please tick here if Benefit Identified by Reviewer but not by company</th>
<th>Please indicate which benefits you believe are justified to be included in the benefit risk assessment by ticking the box</th>
<th>Please explain your main reason for inclusion or exclusion of the benefit parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**3.2 List all the RISKS as documented** *(This prefills summary 8.3.2)*

<table>
<thead>
<tr>
<th>List all risks of treatment for this indication as inferred in the submission</th>
<th>Please tick here if Risk Identified by Reviewer but not by company</th>
<th>Please indicate which risks you believe are justified to be included in the benefit risk assessment by ticking the box</th>
<th>Please explain your main reason for inclusion or exclusion of the risk parameter</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
PRACTICAL USE OF THE BR TEMPLATE

- Justifying the relative importance and contribution of each benefit and risk to the eventual decision

UMBRA framework Steps 4, 5 & 6

<table>
<thead>
<tr>
<th>5.1 Benefits</th>
<th>Relative Importance (weighting) Using selected relative importance system</th>
<th>Valuing the options</th>
<th>Comment on strength and uncertainty of benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populated from 3.1</td>
<td></td>
<td>Investigated product Comparator Placebo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.2 Risks</th>
<th>Relative Importance (weighting) Using selected relative importance system</th>
<th>Valuing the options</th>
<th>Comment on strength and uncertainty of each risk</th>
<th>Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populated from 3.2</td>
<td></td>
<td>Investigated product Comparator Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PRACTICAL USE OF THE BR TEMPLATE

- Detailing the discussion on the uncertainties on the clinical studies and relating to the context of the request

<table>
<thead>
<tr>
<th>4.4 Uncertainties (Benefits &amp; Risks) for pivotal and non-pivotal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.4.1 Discuss the choice of dose, comparator and endpoints (including surrogates as appropriate)</strong></td>
</tr>
<tr>
<td>Comment: ______________________</td>
</tr>
</tbody>
</table>

Was the comparator used relevant for the jurisdiction/Standard of Care? Please select

Please note 4.4.6-4.4.9 relate specifically to risks

<table>
<thead>
<tr>
<th>4.4.6 Are there known or potential interactions between this product and food/drugs?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please select: __________________</td>
</tr>
<tr>
<td>Comment: ______________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.4.9 Please comment on the risk with respect to the indicated product versus standard of care:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

- **Appropriateness** of study design, comparators and efficacy endpoints
- **Validity** of scales and measurements
- **Consistent trending** across studies
- **Negative studies**
- **Interactions** with drugs and food
- **Potential off-label uses and abuse**

**UMBRA framework Step 6**
PRACTICAL USE OF THE BR TEMPLATE

- Incorporating visualisation as component of effective communication

Section 6. Visualisation
If available please provide in this section a copy of any visualisation used to illustrate the benefit risk of product (e.g. forest plot, tornado diagram etc.)

Adobe Acrobat users can click here to attach a file: Attach a file (Note: this will not activate in Adobe Reader)

Click in the space below to upload an image: (jpeg, gif, png) (Available to both Adobe Reader and Acrobat users)

UMBRA framework Step 7
PRACTICAL USE OF THE BR TEMPLATE

- Incorporating the contribution of risk minimization plans and other solicited expert opinions (stakeholders’ perspectives)
- Expert judgment and concluding decision

7.4.3 Describe outstanding issues, and other significant information (e.g., submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (e.g., advisory committees, scientific experts, patients, consumers, consumer advocates, and other stakeholders)).

**UMBRA framework Step 8**

7.4.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage.
OUTCOMES FROM THE CONSORTIUM

- Provided a formal structure to benefit-risk assessment
- Guidance and training for new evaluators
- Setting internal standards and consistency for decision-making
- Aligns to current concept of regulatory processes
- Enhances clarity of decision-making process
- Proper documentation
- Potential for harmonisation and collaborative work
- Systematic articulation of each benefit and risk, and their relative importance provides consistency
- Clear communication and visualisation of benefits and risks to various stakeholders
OUTCOMES FROM THE CONSORTIUM

• **Aligns** to current concept of regulatory processes
• Does not challenge the **scientific rigor** of benefit-risk assessment
• Enhances **clarity** of decision-making process
• **Proper documentation**
  • Improves transparency
  • Improves effective communication
  • Serves as reference to enable consistent basis
  • Promotes governance and provide an audit trail
• Potential for **harmonisation**
OUTCOMES FROM THE CONSORTIUM

• Identified changes required to help achieve its objective in documenting and communicating benefit-risk decisions

• Clarifications required are mainly for the intention of the BR Template and further guidance in documentation, especially weights and values

• All the agencies rated the BR Template as fair or good with regard to ensuring consistency in decision-making through improving regulatory memory.

• It can act as an audit tool and contribute to post-marketing activities
OUTCOMES FROM THE CONSORTIUM

Unique features of the BR Template:

• Listing of benefits and risks identified for the assessment of BR balance
• The reasons for including and excluding the benefits and risks considered
• Assigning relative importance to the values
• Accommodates visualisation/graphical presentation of outcomes
• Structured, guiding questions for discussing the considerations and basis of decision
OUTCOMES FROM THE CONSORTIUM

• Willingness to share the completed template and the summary section with stakeholders
  • Currently restricted by the lack of MOU and conditions of confidentiality
  • Patients and media may potentially benefit from the relative ease of understanding
• Led to hypothesis of using the Summary portion as a stand-alone tool
  • Consideration for maturing markets in documenting and communicating BR decisions
Summary Template for the Benefit-Risk Assessment of Medicines

Professor Stuart Walker, Founder
Dr Neil McAuslane, Director
Centre for Innovation In Regulatory Science

Participant(s):
HSA - Singapore

Compound Identifiers

Product name/ Brand name / Generic name

Active Ingredient(s)/ Strength(s)/ Dosage form:

Proposed Indications

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<td>3.1 Identified Benefits and Risks</td>
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<tr>
<td>7.1 Conclusion</td>
<td>Go to Page</td>
</tr>
</tbody>
</table>
REVIEW OF THE BR SUMMARY TEMPLATE

• 12 reviewers in HSA, representing the agency of an emerging market

• Used recent completed applications to transfer relevant information into the BR Summary Template

• Fit for purpose in documenting relevant information supporting decision and the benefits and risks considered

• Found appropriate to document study outcomes and overall conclusions

• Willingness to share the completed template with stakeholders, but may require customising the material if meant for laypersons
POTENTIAL CHALLENGES

• Effort in training
  • Understanding and application of relative importance/weights in benefit-risk assessment is required
• Visualisation
• Complying to the use of the template
• Duplication of work
  • Enhancing the quality should not add to the quantity of work
  • Add-on or replace existing reports?
• Consider IT enhancements to replicate information
• Buy-in from users and support from management
• Impact to the entire decision-making procedure
POTENTIAL CHALLENGES

- Differences inherent to the agencies’ processes and regulatory model
- Converging approaches does not mean a harmonised regulatory decision among agencies
- Different medical needs, clinical practices and risk tolerance
- Different culture and legislative requirements
- Recognise the varying scientific capabilities within and among the agencies

…but they are both fruits
POTENTIAL CHALLENGES

The Stakeholders

Within agency
- Applicant/Industry
- HTAs/Payors

The regulatory authority

Healthcare professionals
- Patients/Consumers
- Other agencies

- Quality decision and accountability
- Effective communication
POTENTIAL CHALLENGES

The Stakeholders

- Applicant/Industry
- HTAs/Payers
- Within agency
- Healthcare professionals
- Other agencies
- Patients/Consumers

- Quality decision and accountability
- Effective communication
THE WAY AHEAD

The Stakeholders

- Applicant/Industry
- HTAs/Payors
- The regulatory authority
- Healthcare professionals
- Patients/Consumers

- Quality decision and accountability
- Effective communication
THE WAY AHEAD

• Aligning and preparing for the evolving regulatory science

• Changes in the BR balance over life cycle of product

• Responding to new documentary requirements e.g. PBRER

• Responding to ICH initiative to include BR discussion in dossier submission

• Adaptive licensing

• Stakeholders’ expectations on transparency and accountability of decisions
THE WAY AHEAD

• Recognise the need to evaluate BR balance and communicate the basis of decision

• Identifying the components of BR Template and incorporate into existing reports

• Ongoing collaboration
  • Publicly available reports?
  • Work-sharing and joint review?

• Impact to the entire regulatory decision-making process
THE WAY AHEAD

• Exploring the impact of the template in Asia
• SABRE (South Asia Benefit-Risk Evaluation), an initiative under CIRS
• consist of agencies from Indonesia, Malaysia, Philippines, S Korea, China and Taiwan
• Potential tool for exchange of regulatory information among the Asian regulatory agencies
ACKNOWLEDGEMENTS

- Centre for Innovation in Regulatory Science
  - Prof Stuart Walker
- Cardiff University
  - Prof Sam Salek
- Consortium members
  - TGA
  - Health Canada
  - SwissMedic
  - Health Sciences Authority
THANK YOU