Regulatory Standards & Liability: Developing the Appropriate Assessment Model for Medicines

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EMA Benefit-Risk Project

British Institute of International and Comparative Law
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EMA Benefit-Risk Project (2009-2011)

Purpose

To develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products
Interviews at six EU Agencies

What is a benefit?
1. Everything good
2. Improvement in health state
3. Real-world effectiveness
4. Clinical relevance
5. Improvement in illness
6. Safety improvement
7. Positive action of drug
8. Meets unmet medical need
9. Positive improvement in health state as perceived by patient
10. Safety improvement
11. Value compared to placebo
12. Change in managing patient
13. Statistically significant effect

What is a risk?
1. All that is negative
2. Adverse events
3. Reduction in quality
4. Kinetic interactions
5. Side effects
6. Serious adverse effects
7. Bad effects
8. Danger for the patient
9. Tolerance of a drug compared to serious side effects
10. Harm
11. Severity of side effects
12. Frequency of side effects

51. Potential or theoretical risks

Why this longer and more heterogeneous list?
Legislation might be a reason
Article 1 of the Directive 2001/83/EC, ¶28

What is a benefit?
- “positive therapeutic effect”

What is a risk?
- “any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health”
- “any risk of undesirable effects on the environment”.
- Risk is ... any risk!
Consider a new heart attack drug

“There is a risk this drug won’t lower your risk and there are risks from taking the drug.”
Consider a new heart attack drug

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Risk 1: possibility you are a non-responder
Consider a new heart attack drug

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Risk 1: possibility you are a non-responder
Risk 2: your probability of a heart attack
Consider a new heart attack drug

“There is a risk this drug won’t lower your risk and there are risks from taking the drug.”

Risk 1: possibility you are a non-responder
Risk 2: your probability of a heart attack
Risk 3: possible side effects
Consider a new heart attack drug

“There is a risk this drug won’t lower your risk and there are risks from taking the drug.”

Risk 1: possibility you are a non-responder
Risk 2: your probability of a heart attack
Risk 3: possible side effects

Which of these risks are ‘balanced’ in a regulator’s benefit-risk assessment?
Clarifying the meaning of ‘benefit’ and ‘risk’

<table>
<thead>
<tr>
<th>Favourable Effects</th>
<th>Uncertainty of Favourable Effects</th>
</tr>
</thead>
<tbody>
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<td>Unfavourable Effects</td>
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</table>
V. BENEFIT RISK ASSESSMENT

1. Describe beneficial effects
2. Identify main sources of uncertainty
3. Describe unfavourable effects
4. Identify uncertainties in the safety profile
5. Describe if favourable effects with their uncertainties outweigh the unfavourable effects with their uncertainties
Work Package 3
Case study 1: 2009 swine flu pandemic

• WHO declares swine flu pandemic ⇐ drug regulators face choice about approving vaccines
  – Wait until more data available on safety and efficacy
  – Decide now to make vaccine available sooner

• Many concerns at the EMA
  – Seriousness of the pandemic: death rate in Europe
  – Efficacy: will the vaccine work?
  – Safety: how safe will it be?
  – How will vaccines affect critical populations?
  – Should we wait for more data before approving vaccines?
Could a decision conference be helpful?

- An opportunity to test modelling as an adjunct to group discussion
- Group of EMA staff engage in decision conference on 1 September 2009
- Purpose is to test applicability of group modelling: *strictly a research exercise*
- CHMP not involved
- Results not reported to CHMP
“The spirit of decision analysis is divide and conquer: decompose a complex problem into simpler problems, get one’s thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem”

(Howard Raiffa 1968, p. 271)
Decision tree model

Assessed probabilities

Numbers of deaths and serious disabilities

24 scenarios
Result: On average, 17,500 fewer deaths for end-of-September decision
What is the relevance for liability?

- The model revealed characteristics of the decision problem that were not obvious at the start
  - Differences in opinion about safety and efficacy probabilities did not change the decision
  - Only if the probability of the disease being moderate rather than severe was more than 0.84, which nobody believed in September 2009, would it be better to delay the decision
- The model made the reasoning and judgements explicit
  - Many scenarios considered about possible futures
  - Probabilities about uncertain events
  - Estimates of deaths and serious adverse events
Case study 2: Acomplia (LSE MSc project at EMA)

active substance: rimonabant 20 mg

Proposed indications:

- Management of multiple cardiovascular risk factors
- Weight management
- Type 2 diabetes
- Dyslipidaemia
- Smoking cessation

- 19 Jun 2006: approved for obesity and over-weight patients.
- 16 Jan 2009: marketing authorisation withdrawn in light of post-approval data on the risk of psychiatric adverse reactions
Multi-criteria decision analysis (MCDA) value tree with value functions and weights
Calculating overall FE/UFE balance

1. Normalise weights so sum = 100

The perfect drug: 15% weight reduction, no side effects: Score = 100
Calculating overall FE/UFE balance

2. Score rimonabant

Absent/1000 = 64

- Weight loss: 33
- Anxiety: 67
- Sleep Disorders: 67
- Mood alterations with Depressive symptoms: 67
- Depressive Disorders: 67
- Irritability Nervousness: 67

6.6

- 23
- 20
- 13
- 36
- 9

0.944
0.921
0.952
0.968
0.969
Calculating overall FE/UFE balance

3. Multiply scores by weights

\[
\begin{align*}
\text{Favourable Effects} & \quad 64 \times 0.33 = 21 \\
\text{Weight loss} & \quad 64 \times 0.944 = 60 \\
\text{Anxiety} & \quad 23 \times 0.921 = 21 \\
\text{Sleep Disorders} & \quad 20 \times 0.952 = 19 \\
\text{Mood alterations with Depressive symptoms} & \quad 13 \times 0.968 = 12 \\
\text{Depressive Disorders} & \quad 36 \times 0.969 = 35 \\
\text{Irritability Nervousness} & \quad 9 \times 0.969 = 9 \\
\end{align*}
\]

\[
\text{Sum} = 96
\]

\[
\frac{\text{Absent/1000}= 6.6}{\text{for rimonabant}}
\]

\[
21 + 64 = 85
\]

Repeat for placebo

\[
96 \times 0.67 = 64
\]
Overall results as stacked bar graph

- Rimonabant better than placebo for weight loss
- Rimonabant very slightly worse for side effects
- This result from data in the initial dossier
Is the result sensitive to the weights on the effects?

A substantial increase in the weight on Unfavourable Effects would be required for the Placebo to be at most just slightly preferred.
Compare rimonabant with placebo

<table>
<thead>
<tr>
<th>FE/UBE Balance</th>
<th>Model Order</th>
<th>Cum Wt</th>
<th>Diff</th>
<th>Wtd Diff</th>
<th>Sum</th>
</tr>
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<tbody>
<tr>
<td>Weight Loss</td>
<td></td>
<td>33.3</td>
<td>46</td>
<td>15.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Irritab_Nerv</td>
<td></td>
<td>6.0</td>
<td>-2</td>
<td>-0.1</td>
<td>15.1</td>
</tr>
<tr>
<td>Mood Alt+DS</td>
<td></td>
<td>8.3</td>
<td>-2</td>
<td>-0.1</td>
<td>15.0</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>23.8</td>
<td>-2</td>
<td>-0.4</td>
<td>14.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>15.5</td>
<td>-3</td>
<td>-0.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Insomnia+SD</td>
<td></td>
<td>13.1</td>
<td>-4</td>
<td>-0.5</td>
<td>13.6</td>
</tr>
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Total: 100.0  13.6
Post approval: new evidence of psychiatric side effects

Double all proportions of unfavourable effects.
Halve weight-reducing effect.

Now rimonabant looks only marginally better than the placebo.

Same weight on Unfavourable Effects, 67
Compare rimonabant with placebo

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Total Sum: 100.0
What is the relevance for liability?

• Both models made the reasoning behind the decision explicit

• The revised model, with new data, confirmed the withdrawal of the drug

• The revised model showed how the combination of unfavourable effects could tip the benefit-risk balance

• The impacts of favourable and unfavourable effects, and their uncertainties require acts of human judgement

• There can be no ‘objective’ determination of the ‘benefit/risk’ balance
What are the implications for regulatory standards and liability?

- Risk-benefit balance (EC Directive, para 28a):
  “An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent.”
- BUT, risk was defined as “any risk”
- No mention of uncertainty in the Directive
- No mention of judgement in valuing favourable effects and the severity of unfavourable effects
- Are new regulatory standards required?
THANK YOU!