European regulatory views on benefit-risk assessment methodologies

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Presentation disclaimer: The views presented are personal
Content

• A short introduction to Benefit/Risk assessment at the EMA
• The new CHMP Benefit-Risk AR template
• Effects Table
• Potential use of quantitative B/R methods in drug evaluation
Marketing Authorisation for Taxotere (docetaxel, 1995)

The Committee for Medicinal Products for Human Use (CHMP) Members have, during the review process, agreed that the application contains sufficient clinical data to support clinical safety and efficacy allowing a positive recommendation for granting marketing authorisation.
Marketing Authorisation for Ninlaro (ixazomib, 2016)
Challenges in benefit-risk assessment

• Approval of drugs in EU is based on concept of positive benefit-risk balance

• Weigh multiple measures of benefit and risk using subjective value judgments

• Need to balance multiple measures of benefit and risk, with uncertainty:
  – Statistical uncertainty (i.e., wide confidence intervals), especially with regard to favourable and unfavourable effects with low incidences
  – Uncertainty with regard to the clinical relevance of the observed effects sizes due to the lack of evidence on hard clinical outcomes

• Publicity about the reasons and rationale that play a part in decisions

Daniels N. Accountability for reasonableness. BMJ. 2000
What has changed

- March 2008: EMA publishes a *reflection paper on benefit-risk assessment methods* with two main recommendations:
  1. Revise the benefit-risk balance section of the CHMP Assessment Report (AR) template
  2. Research methodologies of benefit-risk balance
     - Involve experts in Decision Theory (L. Phillips, B. Fasolo)
     - Improve consistency, transparency and communication of B/R
     - Switch from “implicit” to “explicit” decision making
The PrOACT-URL framework

⇒ A qualitative framework for structured decision making

1. Problem - Determine the nature of the problem and its context
2. Objectives - Establish objectives and identify criteria of favourable and unfavourable effects
3. Alternatives - Identify the options to be evaluated against the criteria
4. Consequences - Describe how the alternatives perform for each of the criteria
5. Trade-offs - Assess the balance among favourable and unfavourable effects
6. Uncertainty - Assess the uncertainty associated with the effects
7. Risk tolerance - Judge the relative importance of the decision maker’s risk attitude
8. Linked decisions - Consider the consistency of this decision with past/future decisions
Benefit-risk assessment report template

- Therapeutic context
- Favourable effects
  - Uncertainty and limitations about the benefits
- Unfavourable effects
  - Uncertainty and limitations about the risks
- Effects Table
- Importance
- Balance of benefits-risks
- Additional considerations on the benefit-risk balance
- Unmet need
- Risk attitude
- Value judgments
- Facts; data
- Justify
- Conclusions
EMA Benefit/Risk Project

Descriptive methods: Effects Table
- Implemented in 2015
- Simple to build, useful compact display
- Can be generally applied, can be used as basis for quantitative methods

Quantitative methods: Multi Criteria Decision Analysis (MCDA)
- Require substantial resources/effort to build model
- Not used yet in actual decision-making
- “Pilot” studies on patient preferences
Why the reluctance?

<table>
<thead>
<tr>
<th>Against</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>The doctor (expert/regulator) knows best</td>
<td>Impact of different stakeholders input (e.g., from patients) can be explored</td>
</tr>
<tr>
<td>Highly subjective; “unscientific”</td>
<td>No more subjective than any intuitive approach; subjectivity is handled explicitly</td>
</tr>
<tr>
<td>Require more effort; words are better than numbers; why change</td>
<td>Minimise bias of intuitive approaches</td>
</tr>
<tr>
<td>Does not reflect mental process</td>
<td>Easy to update; numbers are clearer than words</td>
</tr>
<tr>
<td>“Black box”</td>
<td>Intuition can lead to error and bias</td>
</tr>
<tr>
<td>High precision is unattainable</td>
<td>Easily understood, transparent</td>
</tr>
<tr>
<td>Oversimplification (“single number”)</td>
<td>Uncertainty can be managed explicitly</td>
</tr>
<tr>
<td>The authority of the decision-makers will be questioned</td>
<td>A single number summary is an abuse of the model</td>
</tr>
<tr>
<td></td>
<td>Regulator’s decisions can be scrutinised</td>
</tr>
</tbody>
</table>

ICH*guidance on B/R assessment

- Avoids advocating for or against specific methodologies for benefit-risk assessment
- “Descriptive” approach generally appropriate
- “Quantitative” approaches encouraged, without specifying a single method for this
- Special situations

* International Council for Harmonisation of Technical Requirements for pharmaceuticals for Human Use

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf
The role of industry

- Significant research in the area over many years
- Number of methods developed
- Have not found their way in regulatory submissions
Possibilities for regulatory guidance

• Scientific advice working party (SAWP) is a multidisciplinary group, comprised of members from different scientific committees of the EMA

• Integrated view on aspects such as
  • quality relating to the development of medicinal products;
  • non-clinical and clinical safety and efficacy relating to the development of medicinal products;
  • the significant benefit of orphan medicinal products;
  • MCDA?
EU experience so far

- Only one SA request with questions on utility of MCDA in upcoming application
- Efforts to standardise evaluation of B/R were welcome by SAWP
- Questions on how parameters included in the model were weighted
- Consideration for patient as well as expert opinion
- Sensitivity analysis necessary
Conclusions

• Important achievements over the last decade
  • Similar descriptive frameworks used by regulators
  • More transparency about the decision
• What role for quantitative approaches?
  • Aversion to quantitative approaches but the environment is changing
  • Openness to explore use of patient preference information
• How to support change?
  • Better understanding of the methods and motivation
  • Exposure to more examples/applications
Thank you for your attention

Further information

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