Benefit Risk Assessment

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How do we reach a positive opinion?

- **Benefit…. What's good**
- **Risks…. What's not so good**

Benefit Risk Balance

benefits

risks

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Why is how we document the B/R balance important?

- **We need to provide a transparent and scientifically sound explanation as to why we find the B/R positive or negative**
- **We need to justify/explain the wording of the indication and all other important information in the SmPC (contraindications, warnings etc).**
- **For whom? Doctors, patients, companies, HTAs etc**

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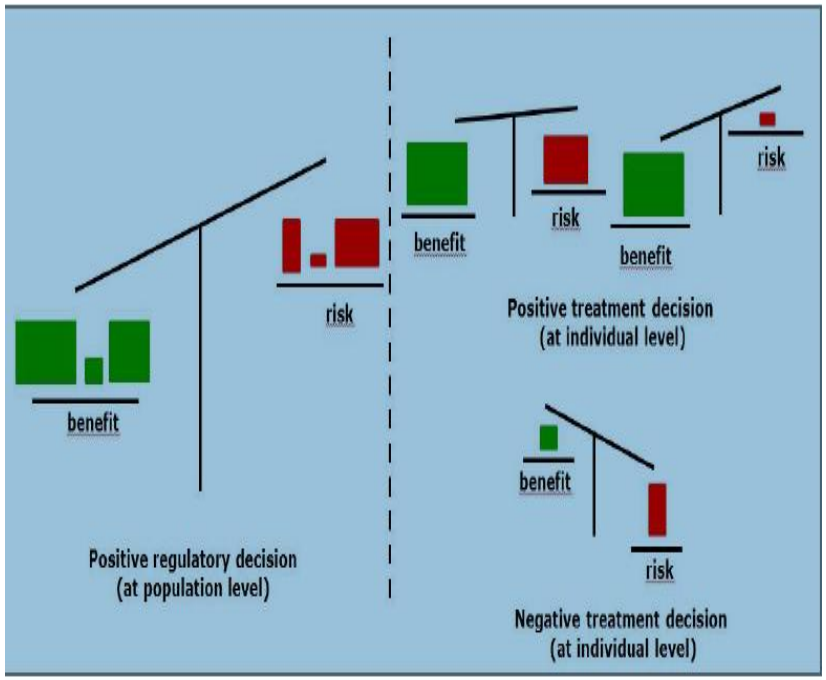
Benefit-Risk Assessment

- ***"The comparative evaluation or weighing of benefits (positive effects) and risks (potential harm) of various medical options for treatment, prophylaxis, prevention or diagnosis"***

- **Benefit-risk balance is the cornerstone of the regulatory approval process and is key to protecting public health and individual patients**
- **However, there is no standard methodology**
- **Each case is different and benefit risk evolves**

Benefit risk is complex



The regulatory decision taken at population level is distinct from the treatment decision taken for the individual patient, and a positive regulatory decision based on objective findings does not exclude a negative benefit-risk balance for an individual. In addition, personal preferences of individual patients may mean that benefits and risks are perceived and weighed differently.

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How do we decide?

The regulators' decision-rule:

- **do the benefits outweigh the risks?**
- **is the degree of uncertainty around B & R acceptably low?**

- **B - H - U (benefits, harms, uncertainty)**

Benefits, Harms, Uncertainty

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Case study: Acomplia
(rimonabant 20 mg)

Jun 2006: approved for obesity and over-weight patients.

("effect was moderate and of clinical relevance for 20-30% of patients")

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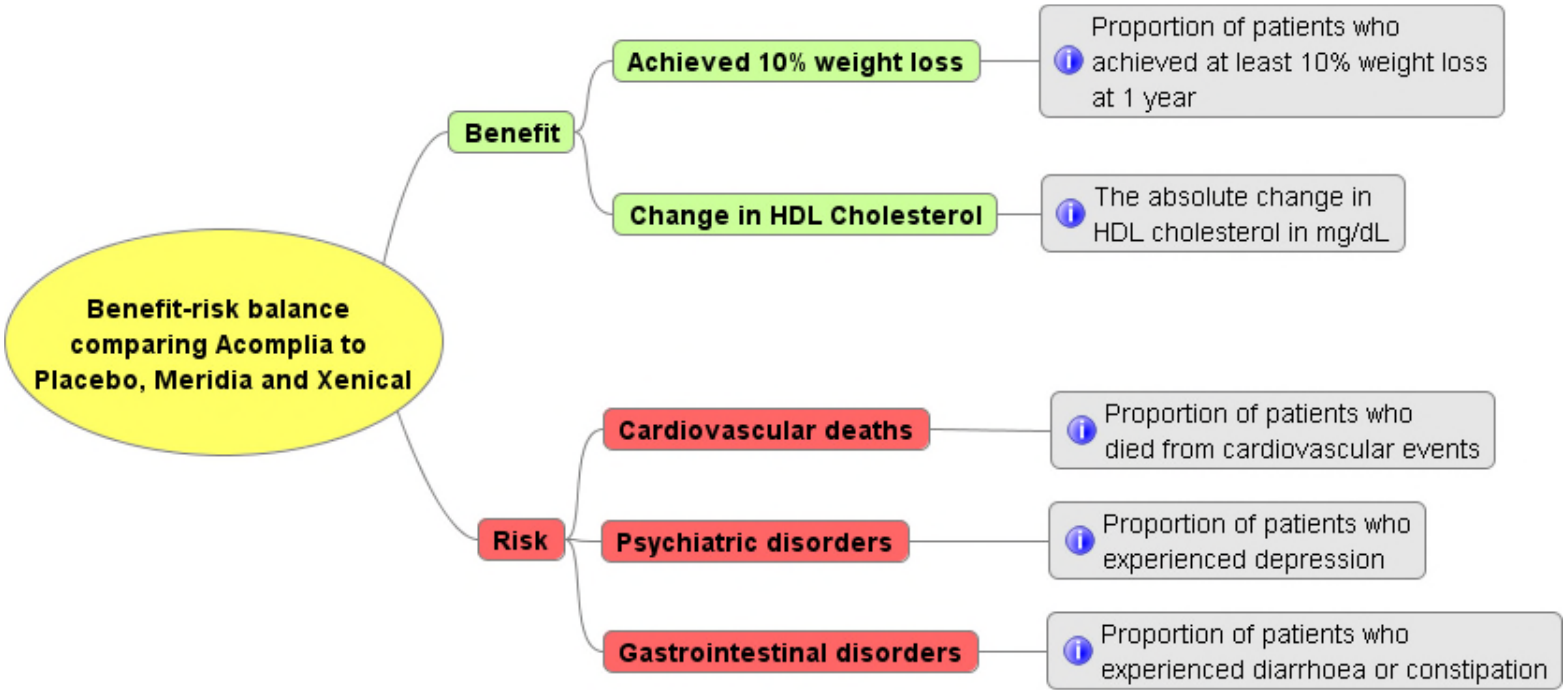
Rimonabant



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Case study: Acomplia
(rimonabant 20 mg)

Jan 2009: marketing authorisation withdrawn in light of post-approval data

("new data indicated a shorter duration of treatment in real life and a reduced beneficial effect…

risk of experiencing the adverse mental effects are higher in patients with comorbidity")

EMA

Benefit-risk methodology

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The European Medicines Agency's opinions are based on **balancing** the desired effects or '**benefits**' of a medicine against its undesired effects or '**risks**'. The Agency can recommend the authorisation of a medicine whose benefits are judged to be greater than its risks. In contrast, a medicine whose risks outweigh its benefits cannot be recommended for marketing.

Weighing up the benefits and risks of a medicine is a complex process, since it involves the evaluation of a large amount of data. In addition, there is always some uncertainty around the actual benefits and risks of a medicine, because they can only be determined by looking at the information that is available at a given point in time.

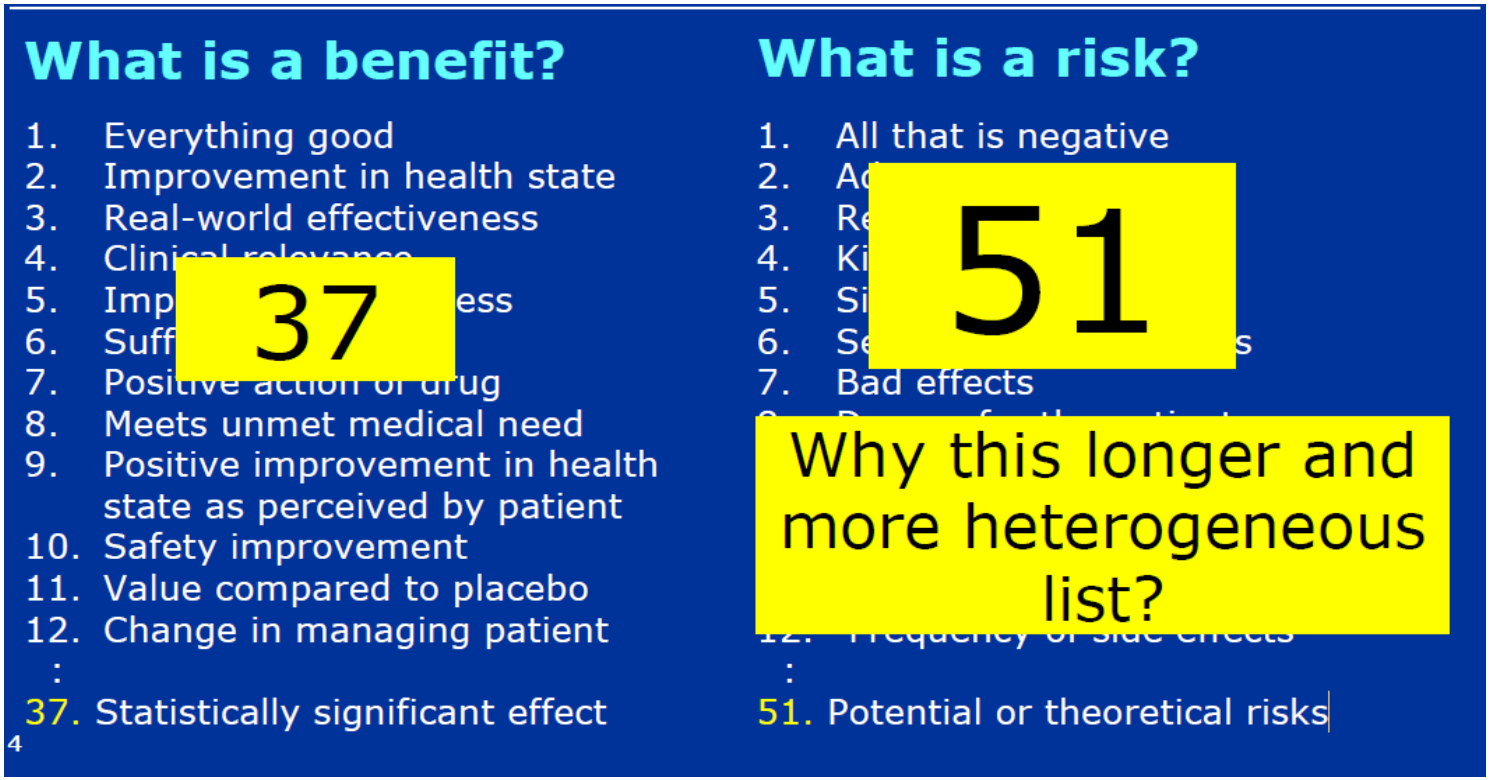
The benefit-risk methodology project

The Agency strives towards making its opinions on the balance of benefits and risks as **consistent and transparent** as possible. To date, however, there is no standard methodology that is used to aid regulatory decisions on the benefits and risks of medicines.

To help address this problem, the Agency began a three-year project on benefit-risk methodology in early 2009. The project aims to identify **decision-making models** that can be used in the Agency's work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit.

The project began on the recommendation of a working group of the Committee for Medicinal Products for Human Use (CHMP) on benefit-risk assessment methods, which met between 2006 and 2008. The working group's conclusions were published in a reflection paper in March 2008.

Initial Workshop to consider B/R



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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" as well as "any risk of undesirable effects on the environment".
- Risk is … any risk!

- **The Unknown**

  As we know,
  There are known knowns.
  There are things we know we know.

  We also know
  There are known unknowns.

  That is to say
  We know there are some things
  We do not know.

  But there are also unknown unknowns,
  The ones we don't know
  We don't know.

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.”**

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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?***

Opinion: Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response

Drug regulatory agencies should ensure that the benefits of drugs outweigh their risks, but licensed medicines sometimes do not perform as expected in everyday clinical practice. Failure may relate to *lower than anticipated efficacy or a higher than anticipated incidence or severity of adverse effects*. Here we show that the problem of benefit–risk is to a considerable degree a problem of variability in drug response. We describe biological and behavioural sources of variability and how these contribute to the long-known efficacy–effectiveness gap. In this context, efficacy describes how a drug performs under conditions of clinical trials, whereas effectiveness describes how it performs under conditions of everyday clinical practice.

Clarifying the meaning of ‘benefit’ and ‘risk’

Favourable Effects	Uncertainty of Favourable Effects
Unfavourable Effects	Uncertainty of Unfavourable Effects

Benefit-Risk Assessment Template

- **Benefits**
  - Beneficial effects
  - Uncertainty in the knowledge about the benefits
- **Risks**
  - Unfavourable effects
  - Uncertainty in the knowledge about the risks
- **Balance**
  - Importance of favourable and unfavourable effects
  - Benefit-risk balance
- **Discussion on the benefit-risk assessment**
- **Conclusions**

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Discussion on the benefit-risk assessment

- **Describe how the balance of favourable and unfavourable effects changes depending on the uncertainties.** For example, a high uncertainty in terms of important favourable effects may generally reduce their value. In terms of unfavourable effects, however, a high uncertainty about the safety will generally increase concerns about certain safety aspects.
- If information is available**, describe how the value judgements could change depending on the perspectives of different stakeholders (physicians, patients, etc.).**
- **Is the benefit-risk balance expected to be the same over the time of treatment?**
- **Discuss different expert views if available**

- **Discuss the need for restrictions to product availability or usage, or any other conditions or measures aiming to improve the benefit-risk balance**
- **Discuss the need for further studies**
- **Conclude on the overall "benefit-risk balance" for the whole indication, and for different subgroups of the indication if necessary**

- Any questions?