EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European regulatory views on benefit-risk assessment methodologies

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Presentation disclaimer: The views presented are personal

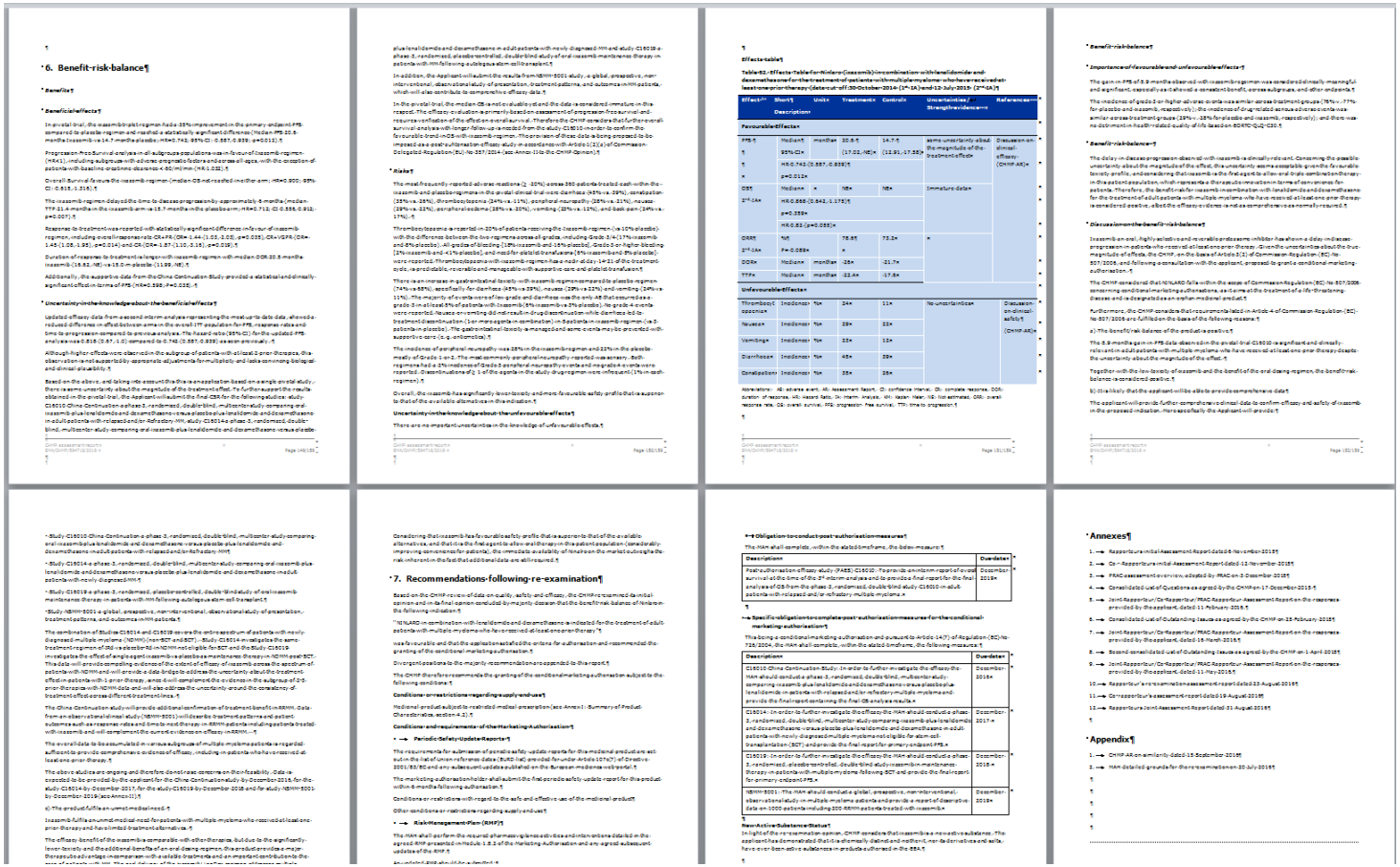
Content

- 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
Eichler HG, et al. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol* (2012)

What has changed

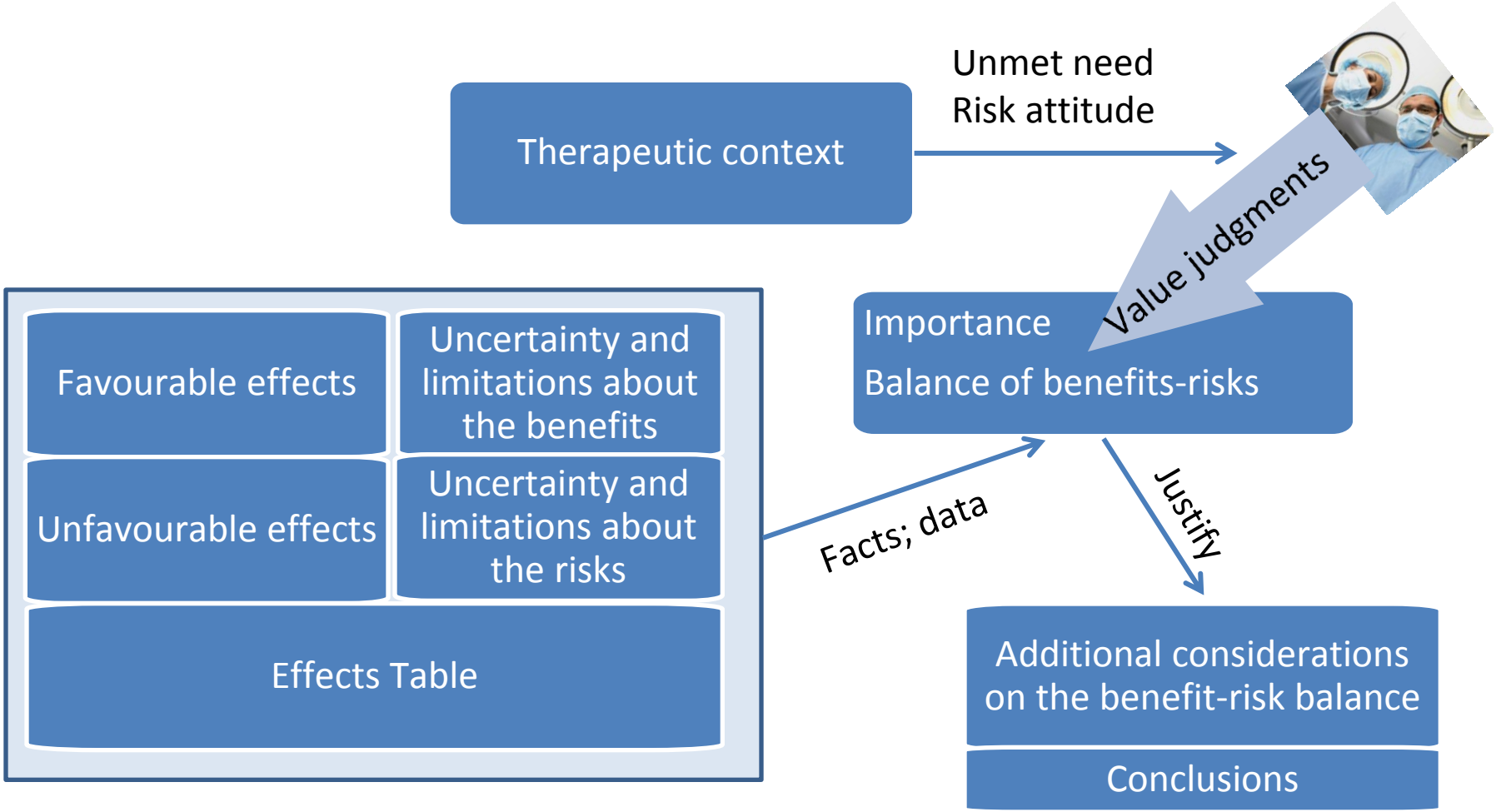
- March 2008: EMA publishes a reflection paper on benefit-risk assessment methods with two main recommendations:
  1. Revise the benefit-risk balance section of the CHMP Assessment Report (AR) template
  2. Research methodologies of benefit-risk balance
     - Involve experts in Decision Theory (L. Phillips, 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

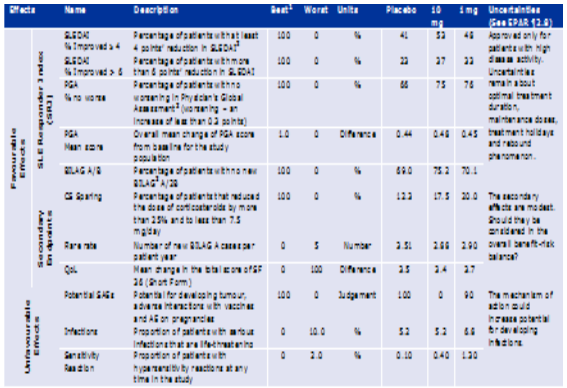
Benefit-risk assessment report template



EMA Benefit/Risk Project

Descriptive methods: Effects Table

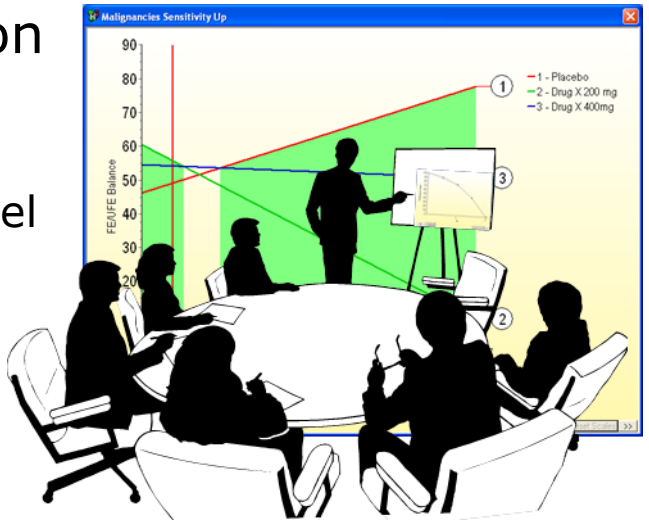
- Implemented in 2015
- Simple to build, useful compact display
- Can be generally applied, can be used as basis for quantitative methods



Effects		Name	Description	Best[1]	Worst	Units	Placebo	10 mg	5 mg	Uncertainties (See EPAR 12.6)
Favourable Effects	SLE Responder Index (SRI)	SLEDAI % Improved ≥ 4	Percentage of patients with at least 4 points' reduction in SLEDAI[2]	100	0	%	41	53	46	Approved only for patients with high disease activity. Uncertainties remain about optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon.
		SLEDAI % Improved ≥ 6	Percentage of patients with more than 6 points' reduction in SLEDAI	100	0	%	23	37	33	
		PGA % no worse	Percentage of patients with no worsening in Physician's Global Assessment[3] (worsening = an increase of less than 0.3 points)	100	0	%	66	75	76	
		PGA Mean score	Overall mean change of PGA score from baseline for the study population	1.0	0	Difference	0.44	0.48	0.45	
		BILAG A/B	Percentage of patients with no new BILAG[3] A/B	100	0	%	69.0	75.3	70.1	
	Secondary Endpoints	CS Sparing	Percentage of patients that reduced the dose of corticosteroids by more than 25% and to less than 7.5 mg/day	100	0	%	12.3	17.5	20.0	The secondary effects are modest. Should they be considered in the overall benefit-risk balance?
		Flare rate	Number of new BILAG A cases per patient year	0	5	Number	2.51	2.68	2.90	
		QoL	Mean change in the total score of SF 36 (Short Form)	0	100	Difference	2.5	2.4	2.7	
Unfavourable Effects		Potential SAEs	Potential for developing tumour, adverse interactions with vaccines and AE on pregnancies	100	0	Judgement	100	0	90	The mechanism of action could increase potential for developing infections
		Infections	Proportion of patients with serious infections that are life-threatening	0	10.0	%	5.2	5.2	6.8	
		Sensitivity Reaction	Proportion of patients with hypersensitivity reactions at any time in the study	0	2.0	%	0.10	0.40	1.20	

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?

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

L. Phillips "Benefit-Risk Modelling of Medicinal Products: Methods and Applications" Benefit-Risk Assessment in Pharmaceutical Research and Development. CRC Press, pages 91-93.

ICH*guidance on B/R assessment

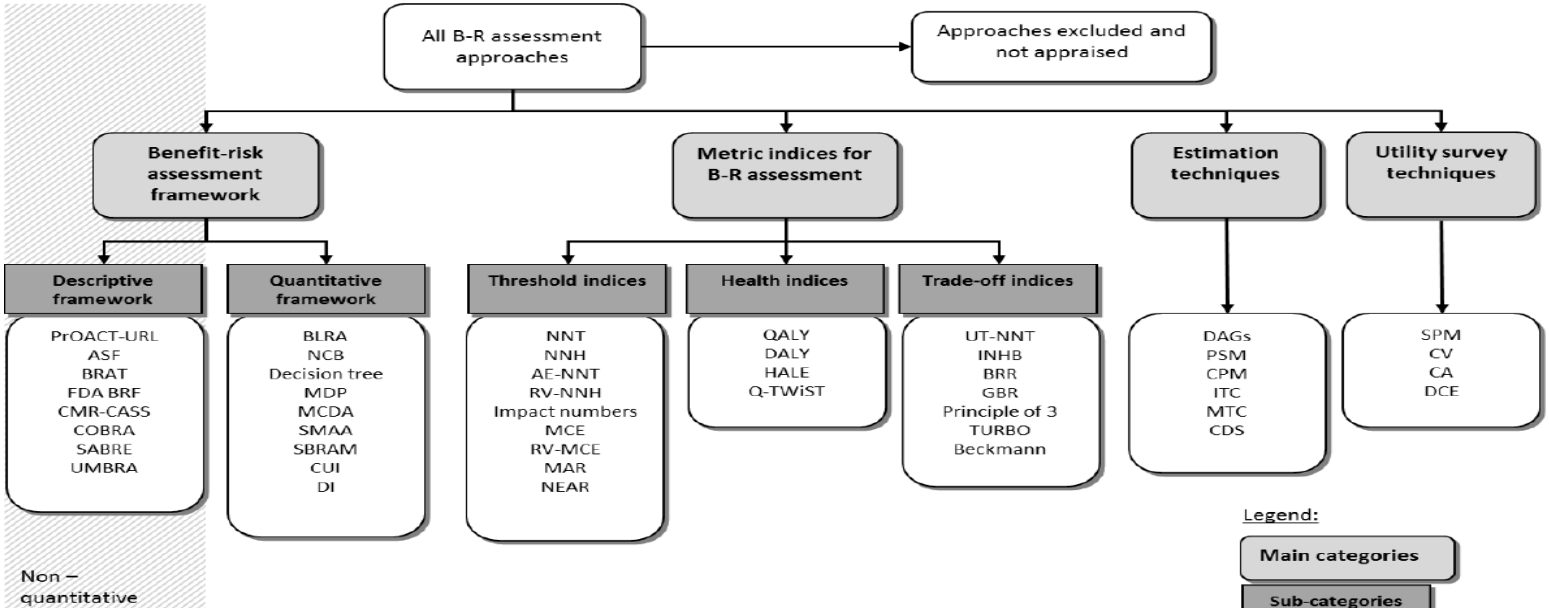
- Avoids advocating for or against specific methodologies for benefit-risk assessment
- "Descriptive" approach generally appropriate
- "Quantitative" approaches encouraged, without specifying a single method for this
- Special situations

* 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



IMI PROTECT Work Package 5

- 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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