EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA experience on the use of the B/R to the effect table: from Rapporteurship to CHMP discussion, to EPAR

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Industry stakeholder platform; London, 3 July 2017

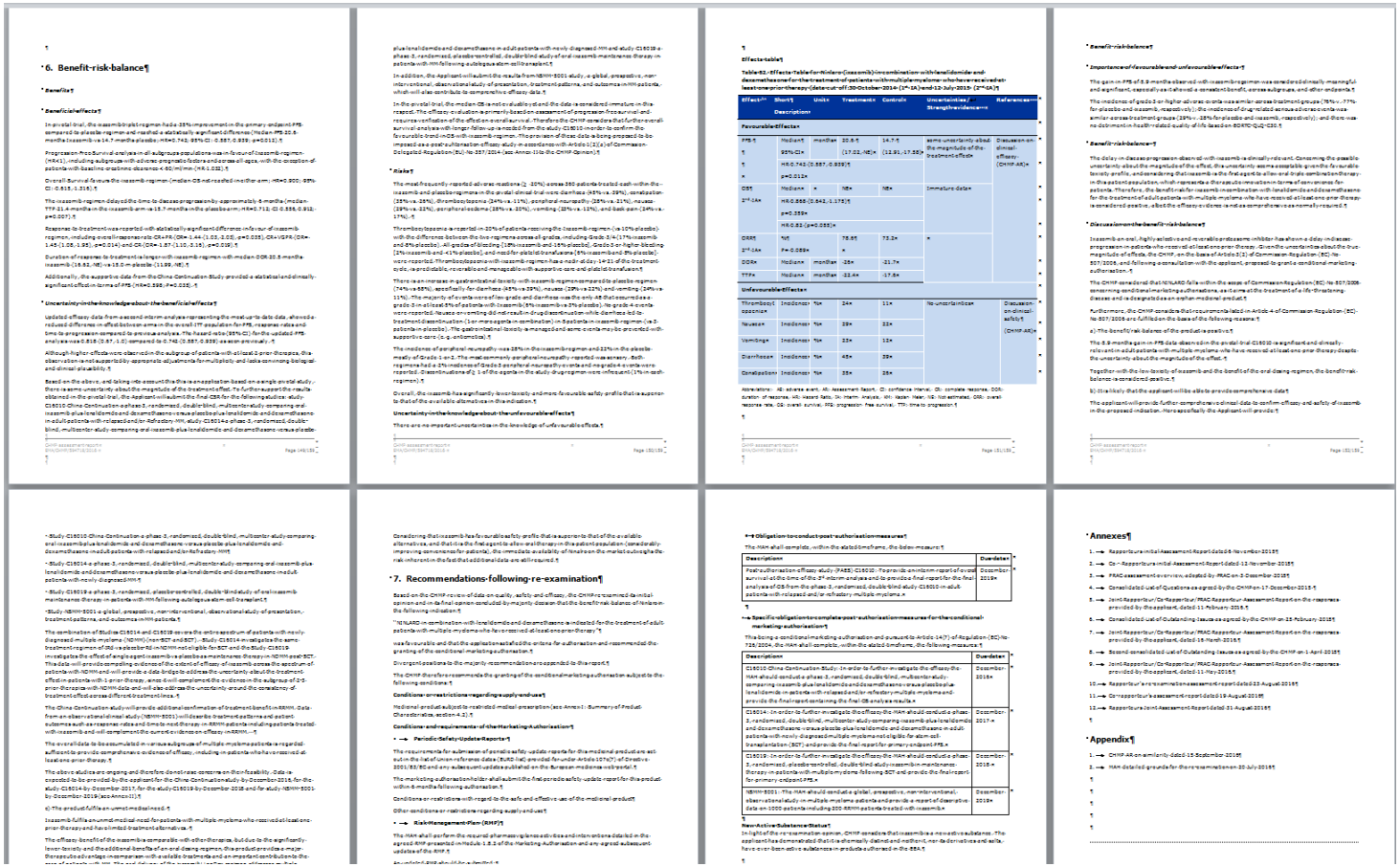
Content

- A short introduction to Benefit/Risk assessment at the EMA
- The new CHMP Benefit-Risk AR template
- Effects Table
- ICH guidance on B/R analysis

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

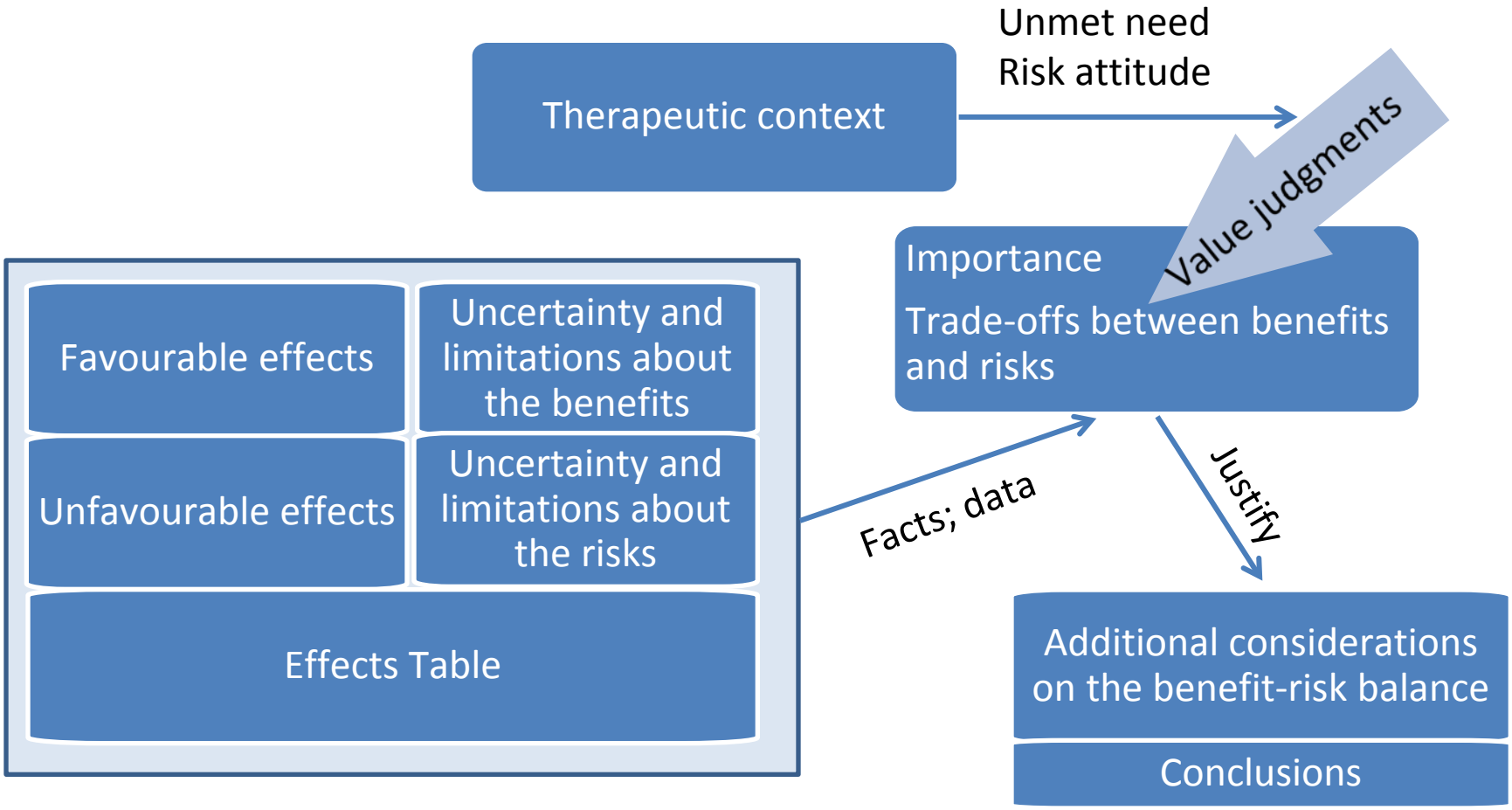
Daniels N. Accountability for reasonableness. *BMJ*. 2000
Eichler HG, et al. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol* (2012)

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



The Effects Table

- Objectives
  - Improve consistency, transparency and communication of benefit-risk assessment
  - Implicit -> Explicit
- Compact display of effects and information for the benefit-risk balance
- Can be generally applied, can be used as basis for quantitative methods
- Pilot phase January 2013-May 2014
- Integrated into assessment reports/EPAR for initial MAs and extension of indications since Q1 2015

	Effect	Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Months	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Pilot: Feedback questionnaire

Six questions to rate (scale: -2 to 2)

	Agree	Slightly agree	Neither agree nor disagree	Slightly disagree	Disagree	Score
The ET improves clarity						1.1
The ET is comprehensive						0.9
The ET is helpful						1.0
The ET is easy to read						0.8
The ET is concise						1.1
The ET does not oversimplify						0.4

One open question for comments

Feedback comments

- Risk of focusing on table and missing the totality of evidence
- Risk of oversimplification outside regulatory camp
- ET not helpful for assessors or assessment process
- Increased workload for assessors
- Does not reflect how the data are interpreted by CHMP
- Not standardized, up to the individual assessor which endpoints/AEs/trials to include
- Difficult to have a good ET for complex data

First ET published on EMA website in June 2015

Effect	Short Description	Unit	Placebo N=131	Lenvatinib N=261	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	3.6 (2.2, 3.7)	18.3 (15.1, NE)	Consistent and significant effect on PFS with a HR of 0.21 (0.14, 0.31)	See 'clinical efficacy' section
OS	Median time from randomization to death of any cause	Months	NE (20.3, NE)	NE (22.0, NE)	The OS data are confounded by crossover with a HR of 0.80 (0.57, 1.12)	
Unfavourable Effects						
Hypertension	Incidence of grade 3 or 4 events	%	3.8	42.9	The association with these risks is further supported by the analysis in the extended safety population The chosen dose of 24 mg is of special concern since it is associated with important levels of dose reductions and interruptions	Numbers presented were taken from the DTC Randomized Safety Set (see 'clinical safety' section)
Proteinuria	Incidence of grade 3 or 4 events	%	0	10.7		
Liver events	Incidence of grade3 or 4 events	%	1	10.7		
Hypocalcaemia	Incidence of grade 3 and 4 events	%	0	4.9		
Diarrhoea	Incidence of grade 3 and 4 events	%	0	9.2		
Fatal AE	Incidence of treatment-related fatal AE	%	0	2.3	Uncertainties linked to low numbers	

Abbreviations: AE: adverse event; HR: hazard ratio; NE: not estimable; OS: overall survival; PFS: progression-free survival
data cut-off dates : efficacy - PFS: 15 November 2013, OS:15 June 2014 ;safety: 25 March 2014.

Subsequent steps

- Adopted “as standard practice”
- EMA produced guidance and training for assessors
- Have monitored implementation over 1st year
- **Now fully implemented**

Guidance document on the content of the <Co-> Rapporteur day <60*><80> critical assessment report

Common issues

- Too much information
  - Double counting
  - Not key effects driving the B/R decision
  - Describe the data *v.* describe the decision
- Discordance between Unfavourable Effects and RMP
- Mismatch between B/R section and Effects Table
- Unfavourable Effects for extension of indications – need to reflect overall risk profile

Double counting…

Example 1

Effect	Short Description	Unit	Active+MTX	PBO+MTX	Uncertainties / Strength of evidence	References
Favourable Effects						
Sustained remission	DAS28(ESR) <2.6 at weeks 40 and 52	%	28.9	15.0		
Sustained LDA	DAS28(ESR) <=3.2 at weeks 40 and 52	%	43.8	28.6		

Example 2

Effect	Short Description	Unit	Treatment (CRd)	Control (Rd)	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Duration from randomization to death	Median (months) HR	Not reached 0.79	Not reached	It did not cross the prespecified early stopping boundary for the interim analysis	AR
Unfavourable Effects						
Deaths	Incidence of death	%	36.2	41.1	7.7% in the CRd arm and 8.5% in the Rd arm died on study. Cardiovascular AEs were reported as the primary cause of death in 10 subjects in the CRd arm and 7 subjects in the Rd arm	AR

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

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH EFFICACY - M4E(R2)

Conclusions

- Important achievements over the last decade
  - Similar descriptive frameworks used by regulators
  - More transparency about the decision
- Effects Table is now central in B/R assessment communication in the EU
  - Provides snapshot of decision making process
  - Facilitates switch from implicit to explicit thinking behind decision
- Balancing necessary complexity and brevity currently the biggest challenge with the benefit-risk analysis section
- Role of quantitative approaches likely to continue to evolve as we gain more experience and confidence in the methods

Acknowledgments: Nikolaos Zafeiropoulos; Hans-Georg Eichler; Francesco Pignatti

Thank you for your attention

Further information

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