EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Benefit/risk assessment of medicinal products

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Presentation disclaimer: The views presented are personal

Content

- A short introduction to Benefit/Risk assessment at the EMA
- The CHMP Benefit-Risk assessment template
  - Effects Table
- ICH Guidance on Benefit/Risk assessment

Definitions

Directive 2001/83

Article 1 – Definition of risk and risk/benefit balance

Risks: any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health

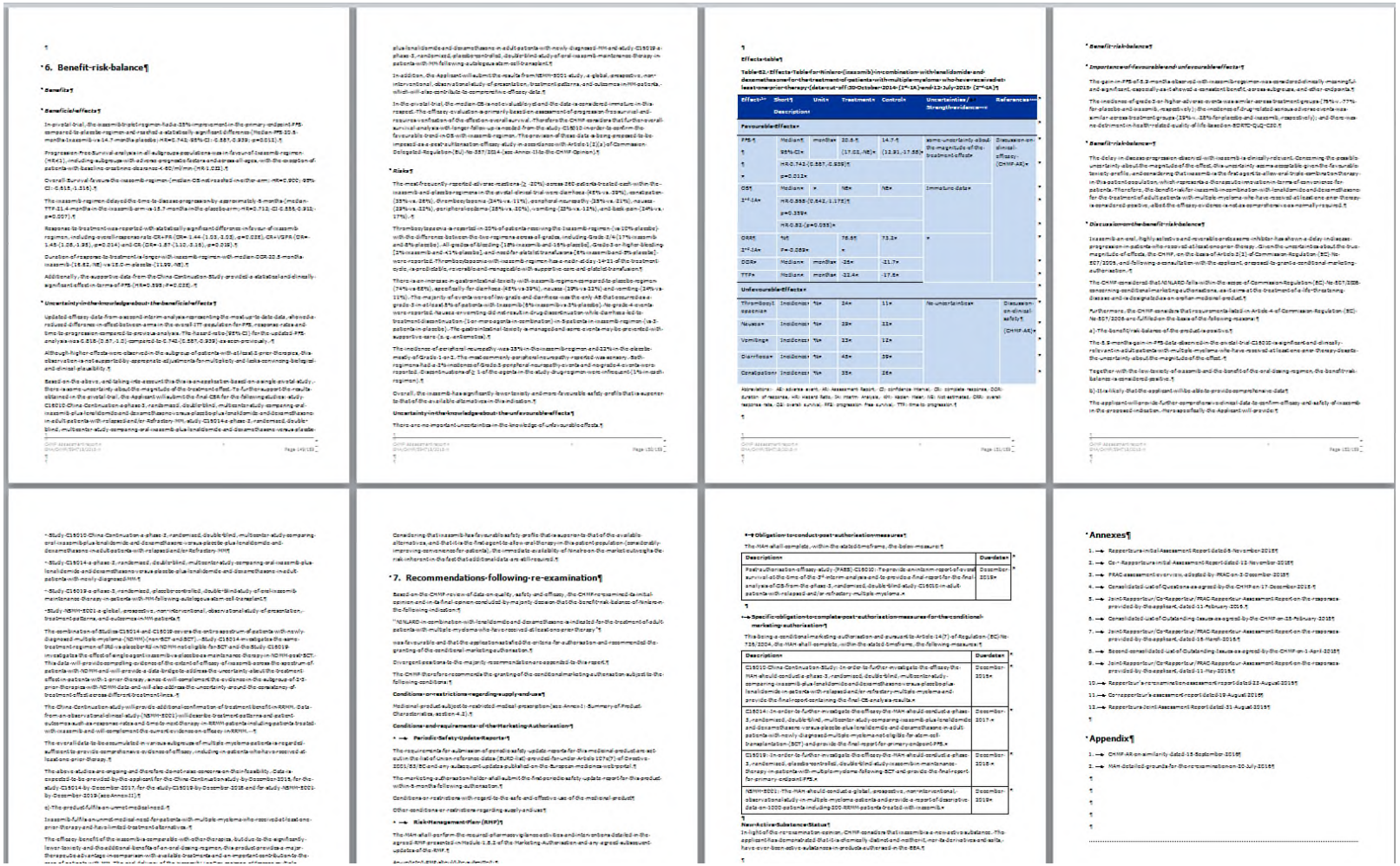
(any risk of undesirable effects on the environment)

Risk/benefit balance: an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined above

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

- EMA/CHMP Working Group set up in May 2006

- 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 Template

Therapeutic context

Unmet need
Risk attitude

Value judgments

Favourable effects

Uncertainty and limitations about the benefits

Unfavourable effects

Uncertainty and limitations about the risks

Effects Table

Facts; data

Importance

Balance of benefits-risks

Justify

Additional considerations on the benefit-risk balance

Conclusions

Implementing PrOACT-URL into the CHMP template

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

Section 5: Benefit-risk

5.0. Benefit-Risk Assessment

5.1. Therapeutic Context

***5.1.1.*Disease or condition**

- State the indication
  - Disease, patient and treatment characteristics necessary and sufficient to describe a population in whom the benefit-risk of treatment is positive
- Describe the aims of therapy

5.1.2. Available therapies and unmet medical need

- Shortly summarise the main available treatment options and the unmet medical need

5.1.3. Main clinical studies

- Design of the main trial(s) and the selected population(s)
- Purpose: frame the problem in terms of evidence basis

Favourbale effects

5.2. Favourable effects

- State the key favourable effects (i.e., primary endpoint and secondary endpoints, point estimates, CI).
- Strive for clarity (e.g., a difference in median overall survival of 6.8 months was observed for treatment X compared to treatment Y, HR=0.8 (95% C.I.: 0.6, 0.9; logrank *P*=.001).
- Avoid interpretation and value judgements (e.g., it was convincingly shown that overall survival was greatly improved for treatment X).
- *What are Key effects? Beware of redundancy (double-counting)*

5.3. *Uncertainties and limitations about favourable effects*

- The description should be factual.
- To be updated during the procedure, if necessary.
- If none: “There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance”

Unfavourable effects

5.4. Unfavourable effects

- State the key unfavourable effects (e.g., severity, duration, reversibility, dose-response relationship; incidence of adverse events leading to withdrawals and/or hospitalisations).
- Strive for clarity; Avoid interpretation and value judgements
- Avoid long lists of individual side-effects (group)
- Consistency with important identified risks described in RMP and SmPC Section 4.8.

5.5. *Uncertainties and limitations about un favourable effects*

- The description should be factual.
- To be updated during the procedure, if necessary.
- If none: “There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance”

5.6 Effects Table

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.

Purpose of the effects table

- The purpose of the Effects Table is to improve the communication of the key effects included in the benefit-risk assessment of new active substances
  - It displays all important favourable and unfavourable effects including all uncertainties and limitations that may affect their clinical interpretation
  - It does not contain any statements regarding the relative importance of the observed effect sizes
  - The final ET published in the EPAR should reflect the final indication and reflect only the data and uncertainties relevant to the intended target population

Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

- Interpret the data using value judgments: e.g., discuss importance in terms of clinical relevance.
  - Which effects are the most important ones given the objectives of therapy in this disease?
  - What magnitude of the effect can be considered as meaningful and how do the observed effects compare to this?
- Surrogate endpoint(s): discuss importance in terms of the true clinical endpoint(s).
- Impact of uncertainties and limitations of the data (as described above)

5.7.2. Balance of benefits and risks

- Describe and explain the tradeoffs: How much is one willing to forgo on one objective in order to improve another objective?
- In theory, may include uncertainties that have an impact on the confidence in the benefit-risk balance (e.g., uncertain value judgments)

5.7.3 Additional considerations

- Explain, justify; regulatory matters (e.g., conditional approval)

Purpose of the effects table

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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

Revised 2.5.6 (Benefits and Risks Conclusions) Structure

2.5.6 Benefits and Risks Conclusions

2.5.6.1 Therapeutic Context

2.5.6.1.1 Disease or Condition

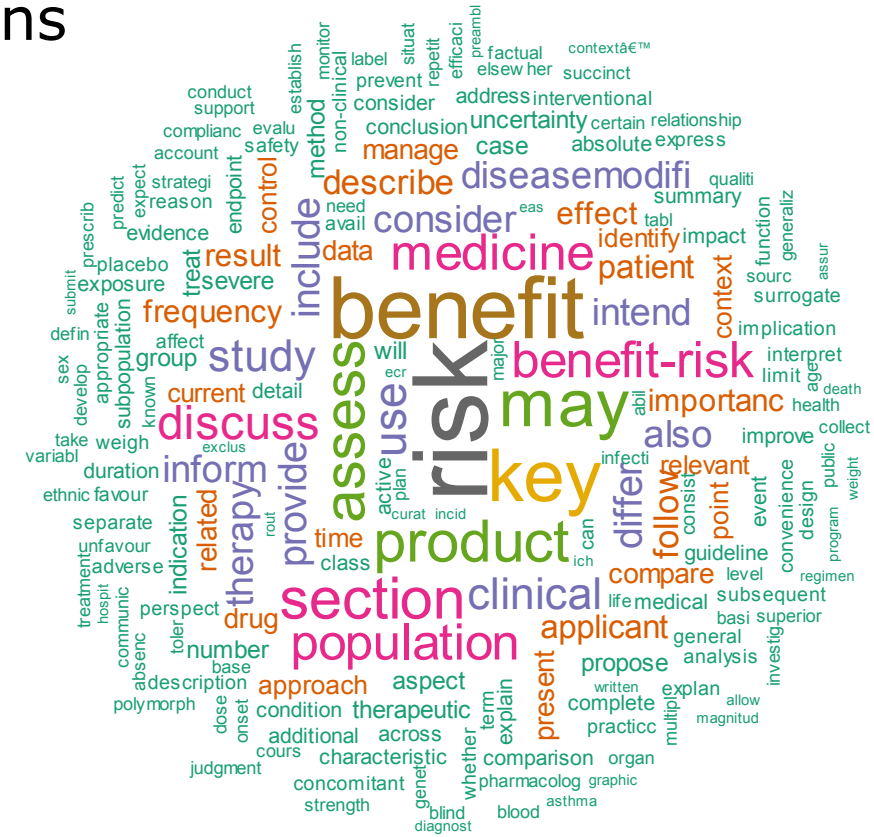
2.5.6.1.2 Current Therapies

2.5.6.2 Benefits

2.5.6.3 Risks

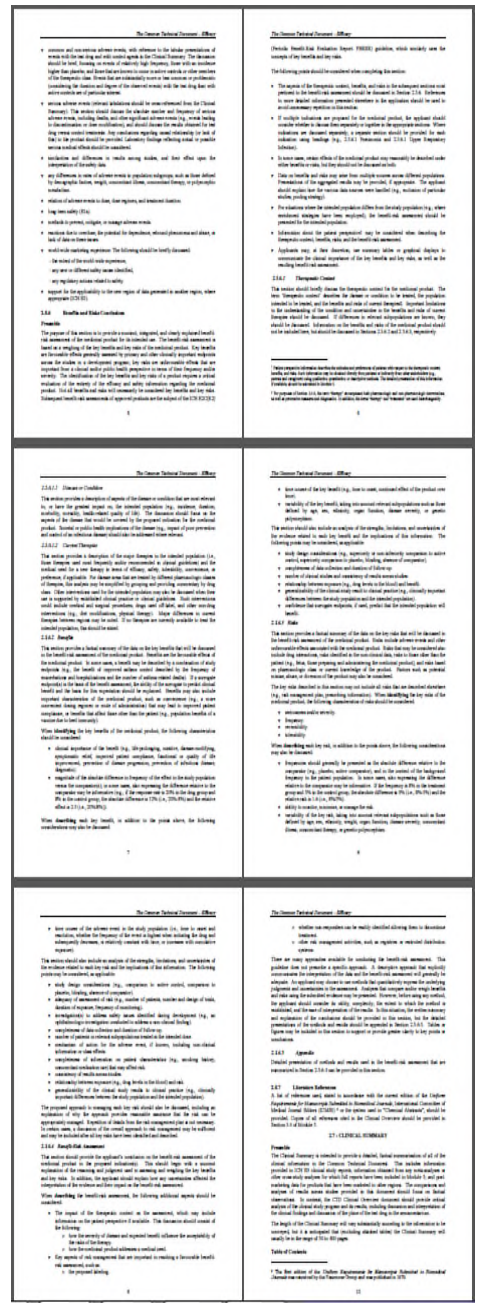
2.5.6.4 Benefit-Risk Assessment

2.5.6.5 Appendix



Outlook

- Benefit-risk assessment is a rapidly evolving field with variations in experience and expertise
- New 2.5.6 captures pan-regional thinking on content, format, and the flexibility to apply different approaches to benefit-risk assessment
- Date for coming into effect (EU): 31 January 2017
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf



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
- Addressing the trade-off between necessary complexity and brevity currently the biggest challenge

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Thank you for your attention

Further information

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