Outcomes of recent EMA/CHMP benefit-risk project (EPAR)

Current progress and future steps

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Background

March 2008 CHMP: Reflection paper on benefit-risk assessment methods with two main recommendations:

1. Revise the benefit-risk balance section of the CHMP Assessment Report template

2. Research methodologies of benefit-risk balance
   - Involve experts, assessors, and specialists in Decision Theory
   - Improve consistency, transparency and communication of B/R
   - Switch from "implicit" to "explicit" decision making

5 Working Packages (WP)

1. Description of current practice

2. Applicability of current tools and methods

3. Field tests of tools and methods

4. Development of tools and methods for B/R

5. Pilot / Development of a training module

Development of tools/methods for B/R (WP4)

Integrated the results from the field tests to a methodology that can accommodate the needs of the various NCAs and the CHMP.

- The PrOACT-URL framework

- Two main tools

  - Effects table (qualitative): *General implementation in templates?*

  - MCDA based approach (quantitative): *In what specific situations?*

- Complexity of our process: *Where and when?*

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

Effects Table (Hypothetical Example)

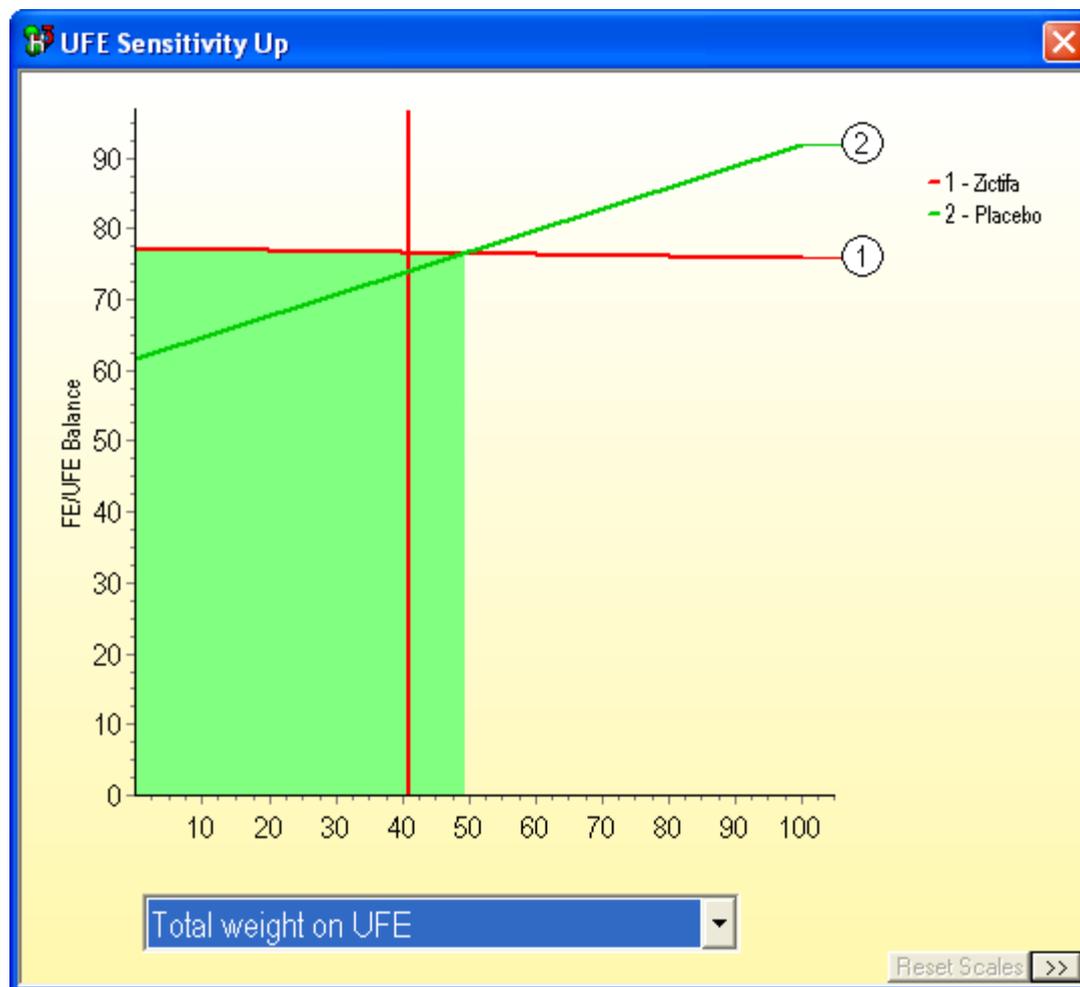|	Effect	Short Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?) Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy? No clear effect on PRO/QoL (missing data)
	PFS (median)	Weibull model	Mo	19.3	30.5	
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	
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 developing further major cardiac SAEs including Torsades de pointe?
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8	

Decision Analysis Modelling (MCDA)

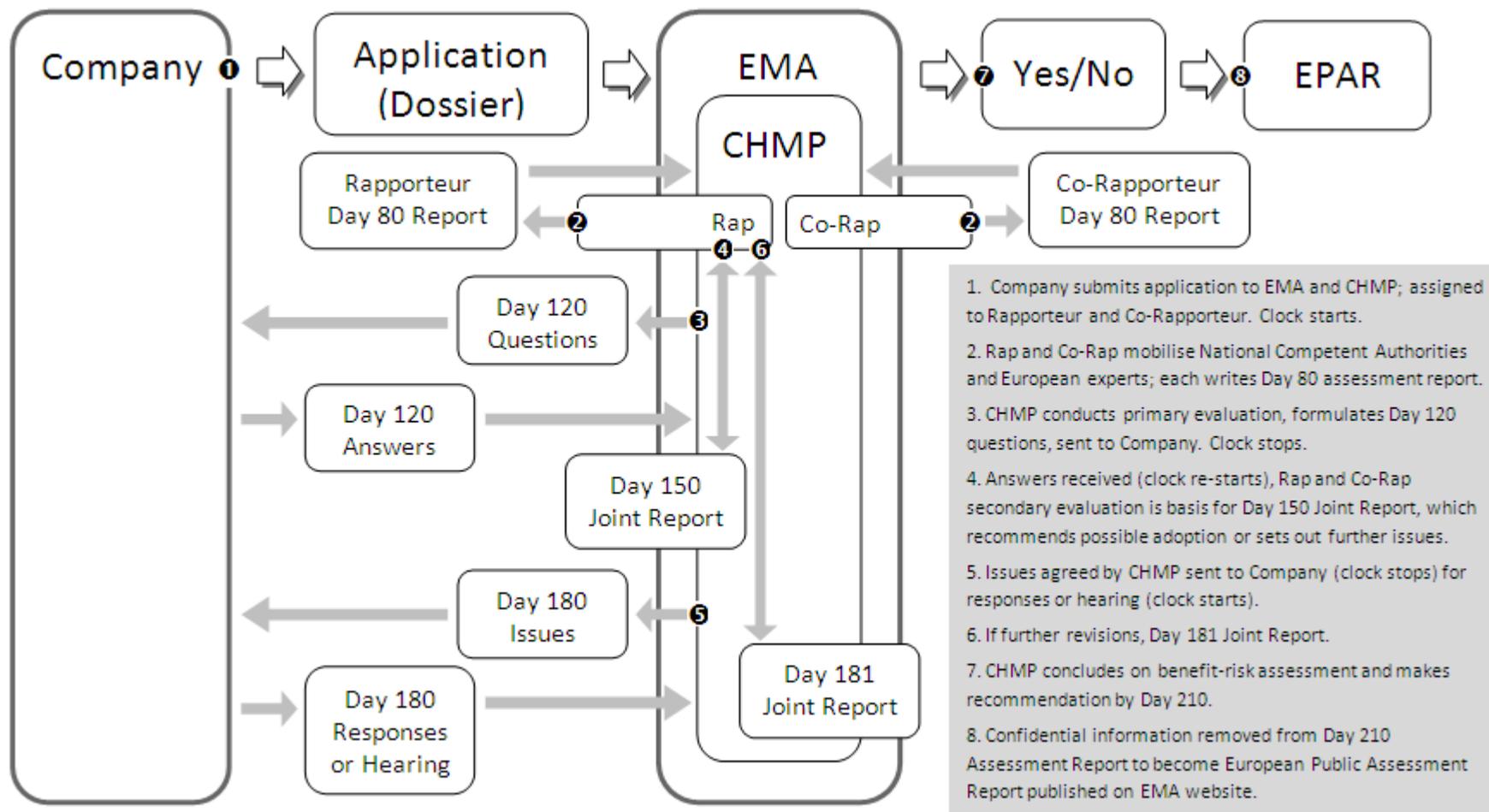Hypothetical example

5. Sensitivity Analysis:

6. Scenario Analysis…

(explore various scores/weights)

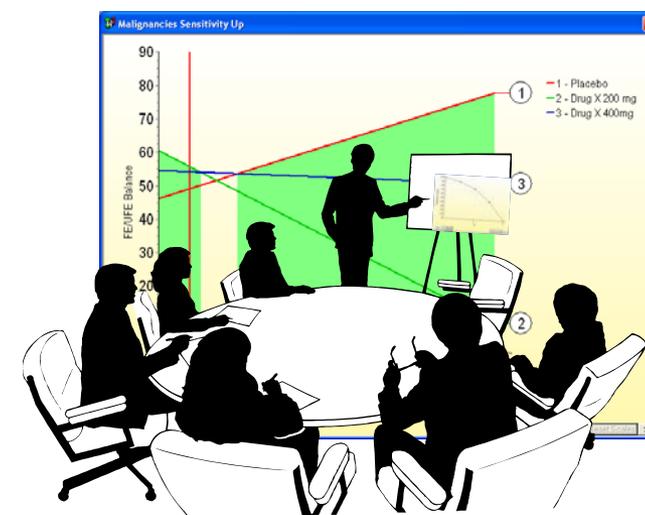# Complexity of our process: *Where and when?*

Company ❶

Application (Dossier)

EMA

❼ Yes/No

❽ EPAR

CHMP

Rapporteur Day 80 Report ❷

Rap ❹—❻   Co-Rap ❷

Co-Rapporteur Day 80 Report

Day 120 Questions ❸

Day 120 Answers

Day 150 Joint Report

Day 180 Issues ❺

Day 181 Joint Report

Day 180 Responses or Hearing

1. Company submits application to EMA and CHMP; assigned to Rapporteur and Co-Rapporteur. Clock starts.

2. Rap and Co-Rap mobilise National Competent Authorities and European experts; each writes Day 80 assessment report.

3. CHMP conducts primary evaluation, formulates Day 120 questions, sent to Company. Clock stops.

4. Answers received (clock re-starts), Rap and Co-Rap secondary evaluation is basis for Day 150 Joint Report, which recommends possible adoption or sets out further issues.

5. Issues agreed by CHMP sent to Company (clock stops) for responses or hearing (clock starts).

6. If further revisions, Day 181 Joint Report.

7. CHMP concludes on benefit-risk assessment and makes recommendation by Day 210.

8. Confidential information removed from Day 210 Assessment Report to become European Public Assessment Report published on EMA website.

Phillips, L. D., Fasolo, B., Zafiropoulos, N., & Beyer, A. (2011). Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discovery Today: Technologies*

7   EMA benefit/risk project: Current progress and future steps

Conclusions To Date

- **Effects Table**
  - Simple to build
  - Improve transparency, communication and consistency
  - Focus discussion on relevant issues

- **Decision Analysis Modelling (MCDA)**
  - Require more resources/effort to build model
  - Allow higher precision, sensitivity analysis
  - May be more relevant in borderline situations, many attributes, no established treatments

Next Steps

- Pilot and Training

  - Pilot and training (WP5) (Q2 2014)

    - Experiment effects table in Rapporteurs' and CHMP assessment reports

  - Endorsement by CHMP (Q3 2014)

- B/R methodology as ongoing activity

  - Continue research for further improvement/development

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