The taming of uncertainty

Uncertainties and coping strategies in the regulatory review of orphan cancer drugs

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Disclaimer: The views presented are personal

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A knowledge paradigm

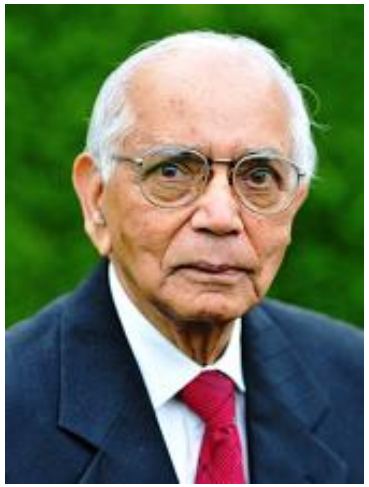
Uncertain knowledge

+

Knowledge of the extent of uncertainty in it

=

Useable knowledge



Source: “Statistics and truth”, 2nd edition, C. R. Rao

Uncertainty

- The lack of certainty
- The state of having limited knowledge
- Vagueness
- Indecisiveness
- Ignorance
- The known unknowns
- Ambiguity
- Lack of clarity

The questions

- What are the remaining uncertainties when a new drug is approved?
  - How are regulators coping with them?
- Can we develop a framework to classify them?

  …or adapt an existing one (why reinvent the wheel?)
- Are there any systematic differences wrt Orphan status* and other variables?

* Orphan status as indicator of prevalence (<1/2000)

EU pharmaceutical legislation

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

To get a new drug in the market you need two things:

1. Sufficiently demonstrated efficacy
2. Favourable benefit-risk (BR) balance

BR balance: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks

- Reflected in the BR section of the European Public Assessment Report (EPAR) published by EMA

  …with a clear separation between effects and uncertainties (2011)

Favourable Effects	Uncertainties of FE
Unfavourable Effects	Uncertainties of UE

A classification framework

Issue	*What we are uncertain about*
Source	*What causes the uncertainty*
Coping Strategy	*How we deal with the uncertainty*

Lipshitz, R. & Strauss, O. (1997) Coping with uncertainty: A naturalistic decision-making analysis. Organizational Behavior and Human Decision Processes, 69, 149-163.

Classifying the "Issue"

what is the uncertainty about?

- Efficacy/Benefits
  - What is the exact magnitude of the effect?
  - How does it work in this subgroup?
  - Is the trial population representative?
  - How does it compare to other available treatments?
  - What happens in the long term?
- Safety/Risks
- BR balance
  - Was this the optimal dose?
  - Can we use a biomarker?
  - What about drug-drug interactions?

Classifying the "Source"

what causes the uncertainty?

- Not enough data

  e.g. limited data in elderly

- Unreliable data

  e.g. single arm study

- Conflicting data

  e.g. divergence between endpoints

- Lack of understanding of relevance of data

  e.g. novel composite endpoint

Classifying the Coping Strategy

how regulators deal with uncertainty?

Coping Strategy	
Acknowledge	Create awareness
	Pharmacovigilance/Risk Management Plan (passive data collection)
	Summary of Product Characteristics (wording)
Reduce	Resolve the uncertainty
	Require further studies/data
	Reasonable timeframe

Ingredients and recipe

- A fit-for-purpose framework
- All new oncology products approved by EMA since 2011
  - ➢ 64 European Public Assessment Reports (EPARs)

    26 orphan and 38 non-orphan
- Uncertainties presented in Benefit-Risk section of EPARs
  - ➢ Coping strategies in BR, Annex II and RMP

Example 1: Zydelig in leukaemia

with large proportions of patients refractory not only to rituximab and an alkylator, but to most lymphoma drugs, including bendamustin (n=62).

Issue: Efficacy – long term

Source: Not enough data

Uncertainty in the knowledge about the beneficial effects.

The pivotal CLL study (i.e 312-0116) was terminated early due to efficacy. There are thus no data on long term efficacy. The magnitude of the treatment effect is therefore not well defined and further follow-up is needed. Further long-term data will be submitted by the applicant within updates of study 312-0116 and as part of the extension study 312-0117 (see annex II of the opinion and RMP).

Risks

Coping Strategy: Reduce – require more data

Unfavourable effects

The most common side effects are infections, neutropenia, increased transaminase, increased triglycerides, diarrhoea/colitis, rash and pyrexia.

Example 2: Kadcyla in breast cancer

Uncertainty in the knowledge about the unfavourable effects

Hepatotoxicity, thrombocytopenia, and neuropathy are the most important recorded AEs, and those that more frequently led to T-DM1 dose reduction in the pivotal trial. Further investigation on T-DM1 induced hepatic toxicity and neuropathy is needed in order to envisage appropriate and effective risk minimisation procedures (see RMP). In addition, a number of AEs known to be associated with trastuzumab use, infusion-related (IRR) and hypersensitivity reactions, severe pulmonary events and cardiac dysfunction, are assumed to occur also with T-DM1 and need to be continuously monitored (see RMP).

Issue: Safety – quantitative

A priority review of missing cases of suspected adverse drug reactions is ongoing in the context of the assessment of deficiencies in the applicant's safety reporting system. In light of the significant clinical benefit of Kadcyla it is considered acceptable to receive the data post-authorisation (see RMP).

Source: Unreliable data

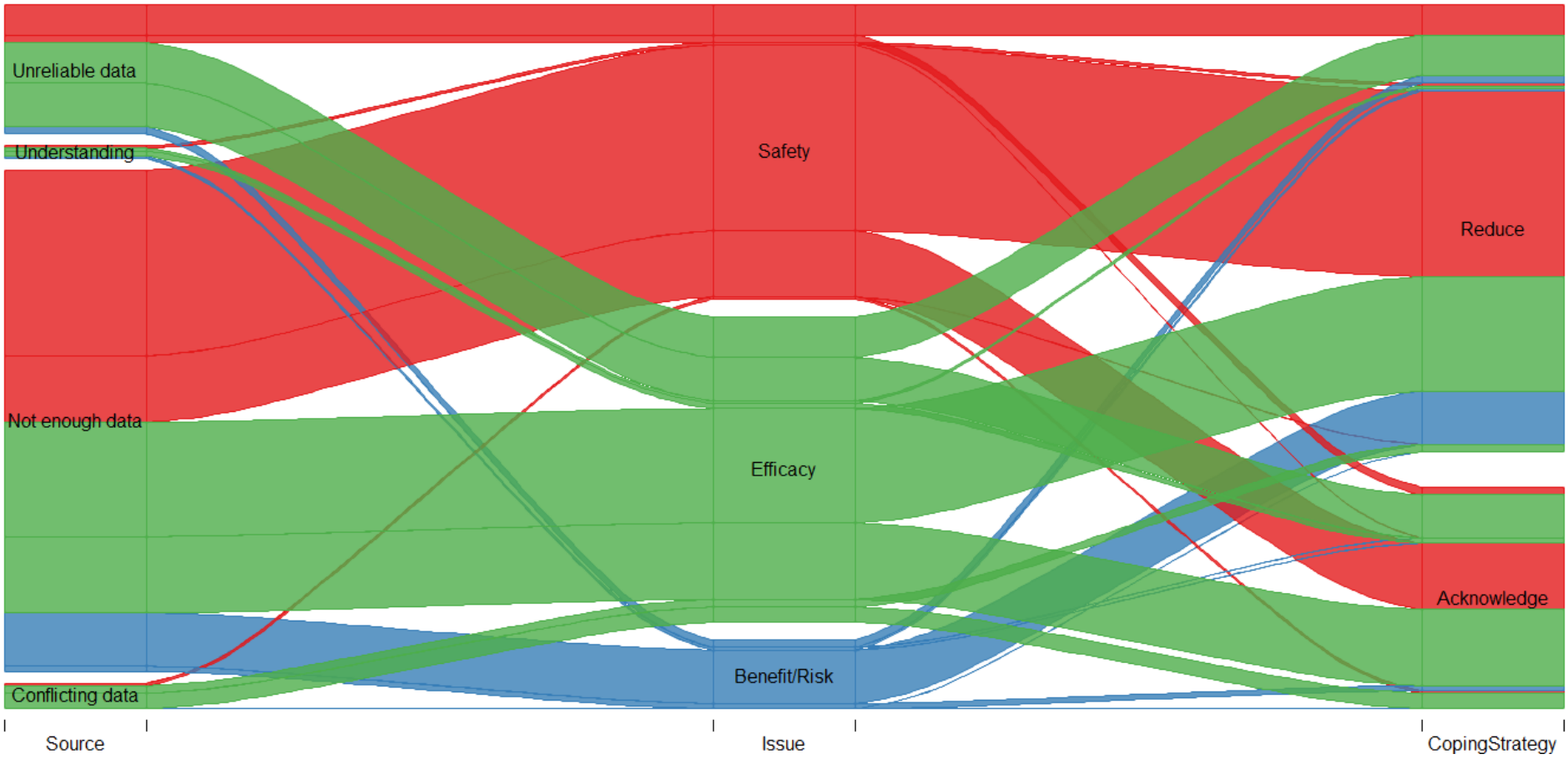
Coping Strategy: Reduce – require more data

Benefit-risk balance

Importance of favourable and unfavourable effects

Trastuzumab emtansine demonstrated statistically significant and clinically relevant efficacy

Alluvial diagram: Source – Issue – Coping strategy



Number of Issues Raised

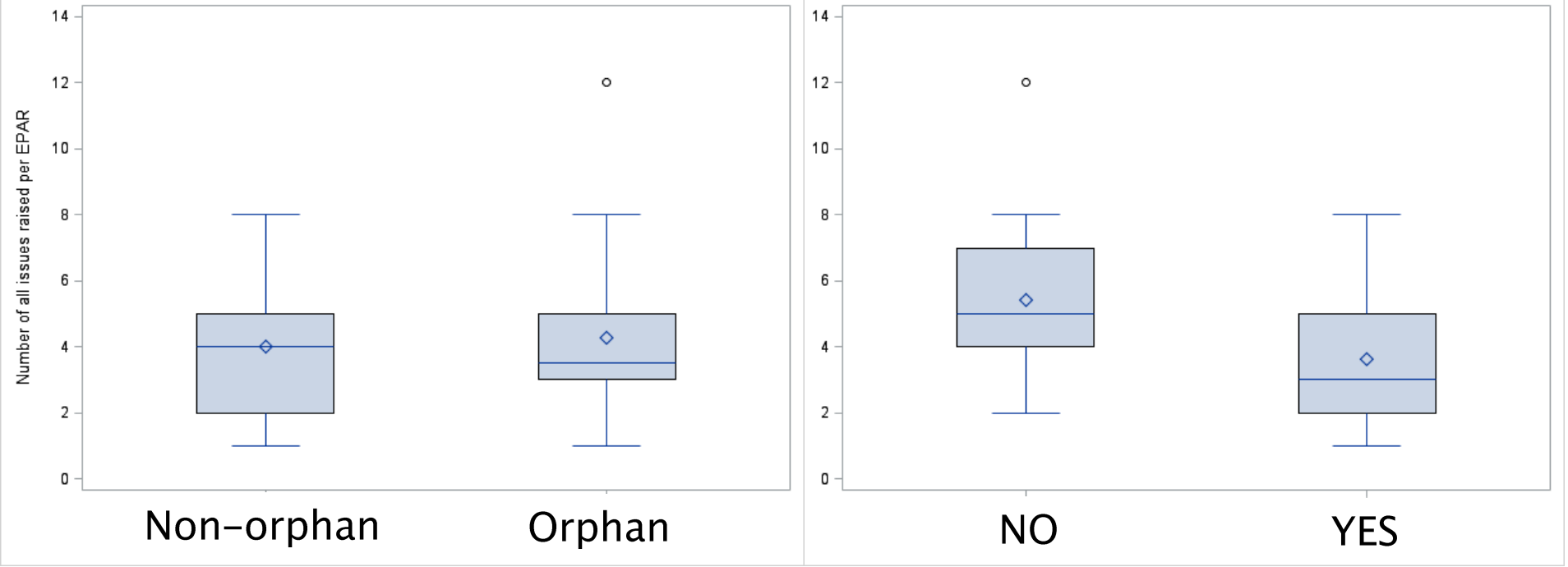
	Non-Orphan (38 EPARs)	Orphan (26 EPARs)	All MAA (64 EPARs)
Issues	152	111	263
Balance of BR	19 (13%)	10 (9%)	29 (11%)
Efficacy/Benefit	66 (43%)	51 (46%)	117 (44%)
Safety/Risk	67 (44%)	50 (45%)	117 (44%)
Source			
Conflicting data	4 (3%)	6 (5%)	10 (4%)
Lack understanding of relevance	2 (1%)	3 (3%)	5 (2%)
Not enough data	126 (83%)	71 (64%)	197 (75%)
Unreliable data	20 (13%)	31 (28%)	51 (19%)
Coping Strategy			
Acknowledge	51 (34%)	36 (32%)	87 (33%)
Reduce	101 (66%)	75 (68%)	176 (67%)

Mean Number of Issues Raised per product

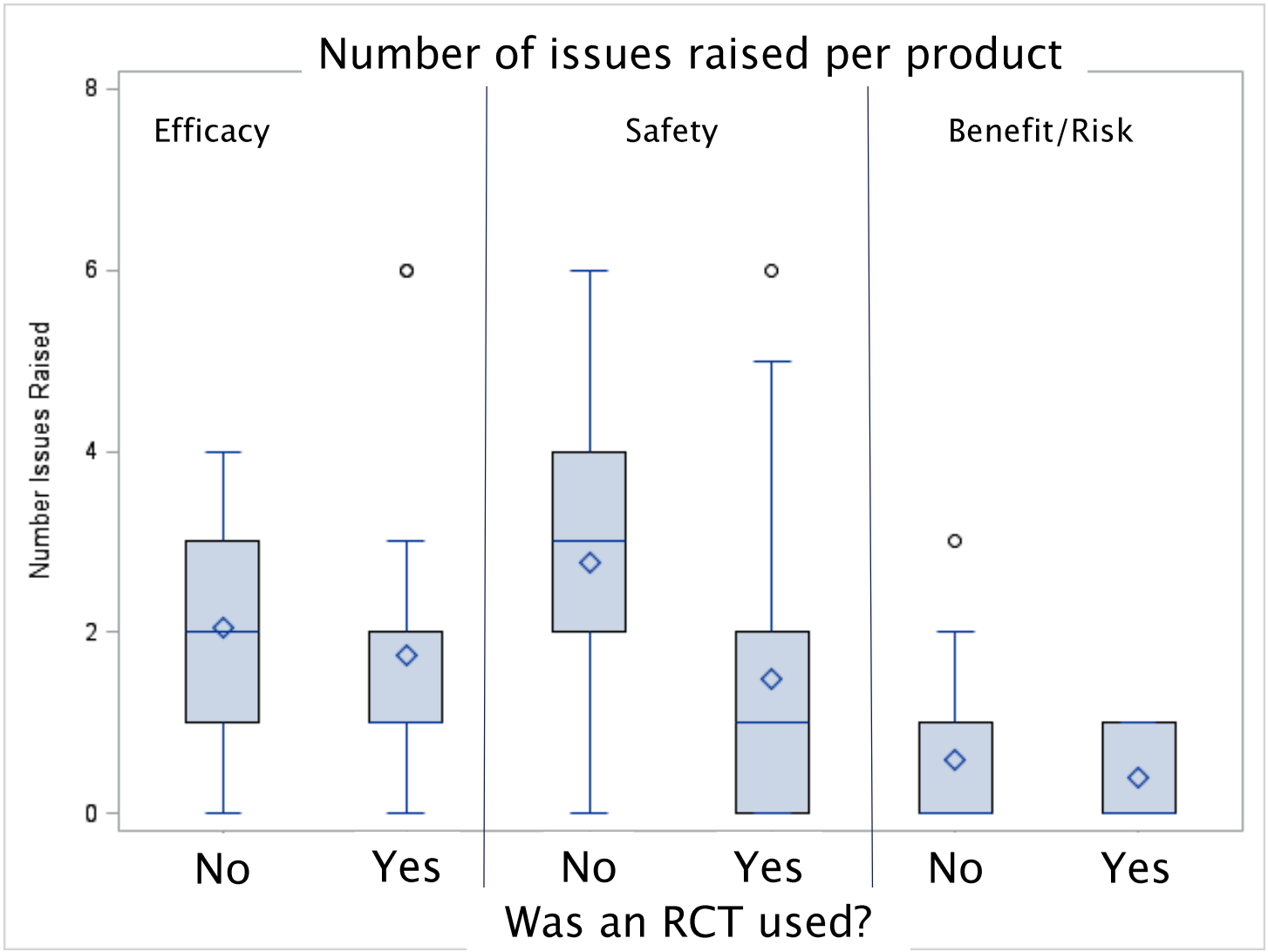
Issues per EPAR (mean number per EPAR±std)			
# all issuess	4.0±1.99	4.3±2.41	4.1±2.15
# efficacy issues	1.7±1.27	2.0±1.28	1.8±1.27
# safety issues	1.8±1.55	1.9±1.57	1.8±1.55
# B/R	0.5±0.51	0.4±0.75	0.5±0.62
Sources (mean number per EPARS±std)			
Not enough data	3.3±1.85	2.7±1.97	3.1±1.90
Unreliable data	0.5±0.80	1.2±1.50	0.8±1.17
Conflicting data	0.1±0.45	0.2±0.51	0.2±0.48
Lack of understanding	0.1±0.23	0.1±0.33	0.1±0.27
Coping Strategies (mean number per EPARS±std)			
Acknowledging	1.3±1.56	1.4±1.68	1.4±1.60
Reducing	2.7±1.66	2.9±2.25	2.8±1.91

Orphan status – Lack of RCT

Number of issues raised per product



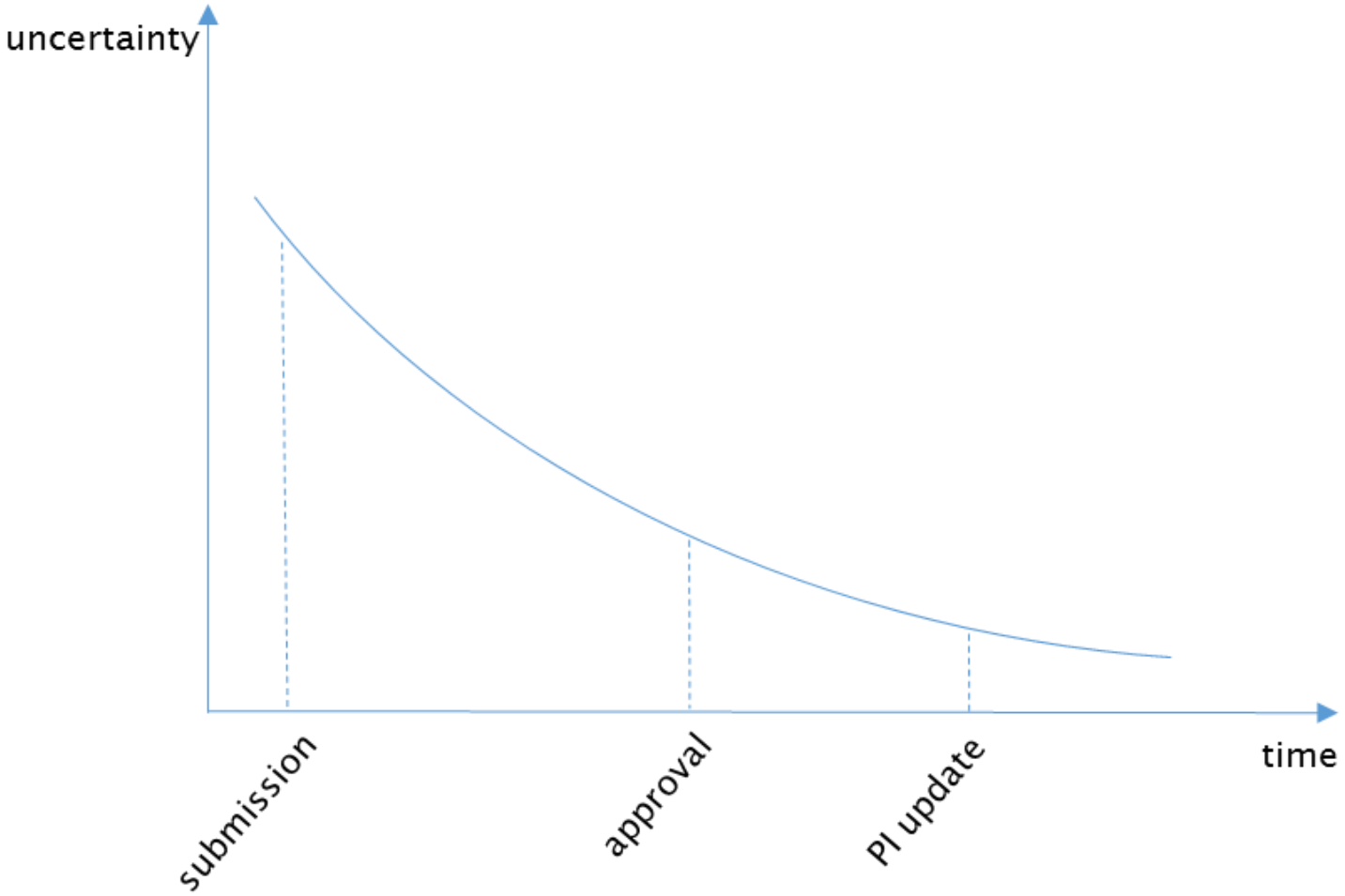
What issues drive this difference?



Main findings

- Several uncertainties pending at time of approval (~4/product)
- Not enough data as main source of uncertainty
  - ➢ Requirement for submission of post approval data
- Safety issues had a higher need for post-approval data
- No major differences based on orphan status
- Lack of RCT associated with additional safety concerns
- Conditional Approvals had a higher need for post-approval data (data not shown)

Drug regulation doesn't stop with approval: the adaptive approach to uncertainty



Limitations of our study

- First ever attempt (as far as we know)
- Are EPARs consistent in presenting uncertainties?
- Do all assessment teams realise same uncertainties?

  "Uncertainty is in the eye of the beholder"
- Are all uncertainties equal?

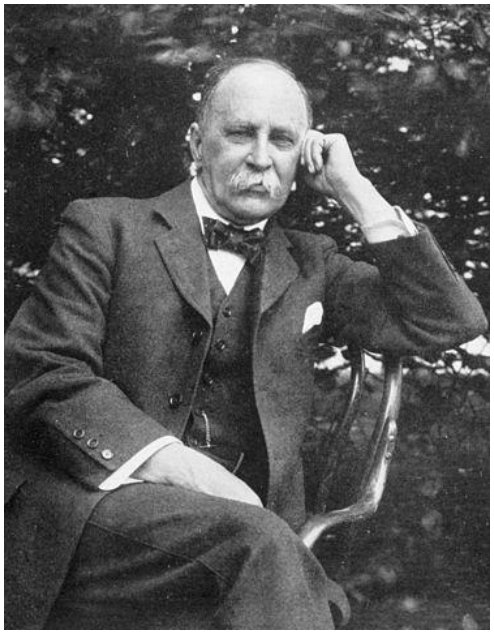
  Counting vs rating
- Non-orphan does not mean non-rare
  - But also, orphan status does not mean "substantially" rare

Work beyond Asterix… (to be decided)

- Longitudinal evolution of uncertainties in a product
  - Apply throughout the review process
  - What happens post-approval?
- Explore other therapeutic areas
- Reproducibility of classification
- Feedback to regulators -> evolve the framework -> incorporate it in the assessment
  - Prospective application?

Thank you for listening!

Medicine is a science of uncertainty and an art of probability.
Sir William Osler



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SEVENTH FRAMEWORK PROGRAMME

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