MHRA
Regulating Medicines and Medical Devices

Structured Benefit Risk – A Regulatory View

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Disclaimer

- The views expressed are personal and reflect that of the presenter, and are not the official position of the MHRA or any other Regulatory Agency.

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- What is driving this?
- What aspect are important?
- An example
- Where might we go in the future?

Do Regulators like Structured Benefit Risk?

- Yes
- To some extent we do it already

Why Do Regulators like Structured Benefit Risk?

- Helps clarify thinking
- Understands Company argument
- See how stakeholders differ by discussing the weight they put on evidence
- People who do post-licensing BR assessment not the same as those who do initial application (within an NCA)
- Same country who does the initial BR assessment no longer does post-licensing BR assessment

What is driving this (I)?

- Transparency
  - To the outside world – see later example
  - Between countries at a European level
  - Within countries e.g. Expert Advisory Groups
- Understand and explain how and why we differ, but come to a common agreement
  - ‘Easy’, relative to quantitative benefit risk

EMA B-R Project - Benefits

1. everything good
2. improvement in health state
3. effectiveness in the real world
4. efficacy in clinical trials (equivalent to positive effect)
5. clinical relevance
6. improvement of illness
7. “drug works”
8. positive action of a drug

- …

21. pre-defined efficacy for a pre-defined population
22. for vaccines, prevention of disease; for antibiotics, elimination of the microbe; for metabolic disease, maintenance; less adverse effects

EMA B-R Project - Risks

1. all that is negative
2. adverse events
3. loss of efficacy (e.g. a company's inability to keep quality intact)
4. kinetic interactions
5. side effects
6. serious adverse effects
7. reduction in quality
8. bad effects.
20. Withdrawal
29. the inverse of short-term and long-term safety

Effects table

Benefits are favourable effects weighted by the clinical relevance

Risks are unfavourable effects weighted by the clinical relevance

GOOD THINGS (Favourable Effects)	Uncertainty of Favourable Effects
BAD THINGS (Unfavourable Effects)	Uncertainty of Unfavourable Effects

Transparency

- Lots of regulators like the effects table
- At least we can now agree on what a benefit and a risk is
  - Weigh them up against each other
- Unclear whether all regulators buy into these definitions
- See also efficacy, effectiveness, relative effectiveness, real world efficacy etc etc

What is driving this (II)?

- Pharmacovigilance legislation:
- “it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product ”

What is needed in a PSUR?

- 16. Signal and risk evaluation
- 16.1. Summaries of safety concerns
- 16.2. Signal evaluation
- 16.3. Evaluation of risks and new information
- 16.4. Characterisation of risks
- 16.5. Effectiveness of risk minimisation (if applicable)

What is needed in a PSUR

17. Benefit evaluation

17.1. Important baseline efficacy and effectiveness information

17.2. Newly identified information on efficacy and effectiveness

17.3. Characterisation of benefits

18. Integrated benefit-risk analysis for authorised indications

18.1. Benefit-risk context — Medical need and important alternatives

18.2. Benefit-risk analysis evaluation

An Example - Xeljanz

- All data available online from EPAR, FDA label
- Potent drug for RA
- 2 doses studied – 5mg, 10mg BID
- Benefits and risks
  - For each dose
  - For each line of therapy
  - With / without MTX/other DMARDs

About RA Trials

- You get a lot of them per package
- Lots of different things you can claim
  - Measure different endpoints at different times
  - ACR20 – RA has ‘improved’ by 20%
  - DAS28 – Disease Activity
  - HAQ – DI - QoL
  - mTSS – joint damage

Data for BR Decision

- 5 studies – See FDA label for more, including:
  - 6-month monotherapy trial, inadequate response to a DMARD (nonbiologic or biologic)
  - 12-month trial, inadequate response to a non-biologic DMARD, added to background DMARD
  - 2 year trial, inadequate response to MTX , added to background MTX
  - 6 months, inadequate response to at least one approved TNF-inhibiting biologic agent, background MTX

EPAR Highlights - Context

- “It was to be used in patients in whom treatment with at least one other medicine known as a biological disease-modifying antirheumatic drug (biological DMARD), had been unsuccessful.”
- Population considered for patients who had:

  Failed DMARD AND

  Failed biological DMARD

EPAR Highlights - Benefits

- “taken together, the data from the five main studies showed that treatment with Xeljanz resulted in an improvement in the signs and symptoms of rheumatoid arthritis and the physical function of patients”
- “studies were not sufficient to show a consistent reduction in disease activity and structural damage to joints, particularly at the lower 5-mg dose of Xeljanz and in the target population of patients in whom treatment with at least two other DMARDs has been unsuccessful”

Benefit Data – FDA label

	Percent of Patients								
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]			**MTX Inadequate Responders[d]**			**TNF Inhibitor Inadequate Responders[e]**		
	Study I			**Study IV**			**Study V**		
N[a]	PBO	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX
	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA[b]	69%	70%	25%	50%	62%	NA	51%	54%

EPAR Highlights - Risks

- “CHMP had major concerns about the overall safety profile of Xeljanz”
- “significant and unresolved concerns about the risk and type of serious infections”
- “safety concerns also included a risk of other severe side effects including certain cancers, gastro-intestinal perforations (holes in the wall of the gut), liver damage and problems with increased lipid (fat) levels in the blood. It was not clear that these risks could be managed successfully in medical practice.”

FDA label

- Boxed warning for serious infections and malignancy
- 5mg dose licensed:

  “indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).”
- mTSS data mentioned as part of trial, but not in results
- See adalimumab, does have mTSS, and a Box

Other jurisdictions

- 5mg and 10mg approved in Russia, Switzerland
  - Swiss is broadly speaking same indication as US (but at both doses)
- 5mg in Japan
- Worldwide, regulators may not be homogenous
  - With Respect to Yes / No decision
  - With respect to Dose
  - With respect to line of therapy
  - With respect to combination

EU Decision

- Weighed up all the benefits
- Weighed up the risks
  - Some had more clinical relevance than others
- Can the risks be managed? If so, might be more positive – uncertainty around them
- Weigh them up against each other
- Did not take into account route of administration
- Not a ‘formal’ Structured BR decision

What might the future hold

- A drug is licensed
- Clear explanation of the benefits and the risks
  - Periodic review can easily incorporate new data
- *A priori* known what level of evidence would cause regulatory action to be taken?
  - Clearly defined endpoints from post-authorisation studies that changes the balance
  - Both point estimates and lower limits of CIs

Problem of pre-specification

- Do not know what we will see in the market place
  - Entire box in the effects table for this
- Often do not know what we will see, safety-wise, in trials
- Independent of any weight you might wish to attach
  - Problem for both quantitative and qualitative BR decision making

More post-licensing issues

- Combining real-world and trial data is challenging
  - Study Design
  - Data Quality
  - Confounding by indication
  - Different patient population
  - Estimation of a ‘placebo’ effect
  - What is the natural rate in RA of AEs
    - With MTX?
    - Without MTX?

Why is the previous slide important?

- Statisticians have a pivotal role to play
  - Not just people who ‘understand numbers’
- We understand data
  - Its strength and limitations
  - How provenance affects interpretation
  - How to combine it appropriately (and when not to)
- All of which are crucial for regulatory decision making

Conclusions

- Drivers of change are here
- Regulators ‘like’ structured BR
- Regulators ‘do’ structured BR
- Some heterogeneity between NCAs around the world
- As a profession we have a key role to play
  - And will continue to do so

Any Questions?

Thank You