Science – how can the scientific information needs of both HTAs and regulatory be accommodated in a common development track?

Workshop on EMA – HTA Parallel Scientific Advice
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Disclaimer

This presentation is based on my own personal views and by no means expressing a company view.

My thoughts should offer a view in order to stimulate a dialogue.

Regulatory authorities and HTA authorities / committees basically have different mandates and methodologies

Regulatory Authorities

- Regional or national
- Evaluate the benefit/risk-ratio of a new therapy based upon quality**,** efficacy and safety
- Grant Marketing Authorization
- Focus on randomized controlled trials to demonstrate superiority or non-inferiority to acceptable standard treatment
  (internal validity)

HTA Authorities / Committees

- National or implemented by private Managed Care Markets
- Assess the relative effectiveness of a new therapy versus other treatment options, which have been defined to be relevant
- Give advice to payers on the additional therapeutic benefit of a new therapy for their reimbursement or coverage decisions
- Focus on RCTs and other available sources of comparative evidence
  (external validity)

Why do we (Health Services Research / Merck Serono) seek for HTA advice?

- To inform investment decisions in drug development
  - to understand, what shapes additional therapeutic benefit in the eyes of the customers
  - to understand the related evidence requirements, and modify our plans accordingly, if feasible
  - To assess the value of information (additional data / studies / analyses to demonstrate relative effectiveness) versus additional investments in terms of time and costs for product development in a permanently changing environment
- To reduce the risks linked to investment in drug development

Current experience with HTA advice

My thoughts in this presentation are based upon some concrete examples:

- Parallel EMA – HTA scientific advice for a specific phase III clinical trial in Oncology
- Multi HTA early dialogue (EUnetHTA JA2 WP7 ED pilots) for a phase III clinical trial program in Multiple Sclerosis
- National HTA advice for a specific Phase II clinical trial in Osteoarthritis (OA)

Parallel EMA – HTA scientific advice / oncology

Evidentiary requirements in an oncology case study

Evidence	Agreement SAWP / HTA	Agreement HTA / HTA	Comments	Reconciliation possible
Primary endpoint	Yes	Yes		
Effect size	Partly	Partly	Some HTA bodies are primarily driven by cost-effectiveness	Yes
Secondary endpoints	Partly	Partly	HTA doesn't distinguish between primary and secondary endpoints	Yes
Radiological assessments	No	No	Standardization versus reflection of routine clinical practice	No (follow SAWP advice)
PRO instruments	No	No	Different requirements related to instruments and data collection time points	Might be Battery of instruments, multiple points, high complexity
PRO analysis	No	No	Different views if approach can lead to meaningful results/conclusions	Might be Complex SAP in case all needs addressed
Comparator	No	No	Different requirements with regards to approved, non-approved, routine practice, guidelines, subgroups	Hardly Only in case study design allow for indirect comparison
Dosing	No	No	Diverging view on doses' benefit risk ratio	No (follow SAWP advice)
Inclusion criteria	No	No	Different views performance status to be considered	No (follow SAWP advice)

Parallel EMA – HTA scientific advice / oncology

How can the different requirements be accommodated in this case study?

- RCTs are the primary source of evidence for both regulatory and HTA agencies
- The standards for clinical endpoint measurement are the same (OS)
  - Although modeling of an average survival gain may be subject to controversial methodological discussions between the different HTA bodies
- When regulatory and HTA requirements are contradictory, global development follows integrated regulatory advice (from different regulatory agencies worldwide)
- Consideration of (country specific) HTA requirements beyond regulatory advice
  - Risk analysis and decision on how “clean” the company wants to keep the pivotal trial to meet regulatory standards (radiological assessments, dose, inclusion criteria, comparator)
  - Estimation of the additional requirements’ impact on the the complexity of the specific study protocol, clinical trial management and data quality versus the value of additional information for relative effectiveness assessment in different markets (PRO, data collection points, definition of patient population / sub-groups, stratification)
  - Understanding, which evidence gaps exist per country and how they can be filled outside RCTs (indirect comparisons, utilities per disease stage, supportive scientific evidence to “match” varying treatment regimens in routine practice with clinical trial standard). Assessment of value of additional information versus investment.

EUnetHTA early dialogue / multiple sclerosis

Some thoughts before the letter of intent was sent out

Opportunities

- Early information of HTA stakeholders about development plan (and potential scientific boundaries within a global strategy)
- Consolidated view on comparators, endpoints, patient populations etc. from the HTA perspective
- Anticipation of HTA authorities' concerns
- Structured and strategic challenging of our clinical development plan; increase the quality of evidence generation during clinical development
- Understanding of European versus US and other regions' requirements for evidence generation; consequences on development time & costs
- Securing fully informed R&D decisions
- Some involvement in disease-specific EUnetHTA assessment guidelines
- Staying on the learning curve in a changing environment

Considerations

- Choices (nonconformance with country-specific advice) to be substantiated and documented
- Deviation from advice may mutually impact EMA and EUnetHTA assessment reports (EPARs improvement project)
- Conscientious decision making required (for example, if advice made a separate European development program necessary, which would not be supportive for the US and other regions)
- Complexity may not be reduced but increased
- National approaches to HTA may not be resolved by EUnetHTA early dialogue
- Any post-approval commitments may remain at the discretion of specific countries (for example real life data collection)

EUnetHTA early dialogue / multiple sclerosis

Evidentiary requirements in a multiple sclerosis case study

- EUnetHTA early dialogue conducted prior to EMA consultation
- EMA guideline available
  - Clinical investigation of medicinal products for the treatment of Multiple Sclerosis
- RCTs are the primary source of evidence for both regulatory and HTA agencies
- Same standards for target patient population and clinical endpoint measurement
- No consensus across HTA countries regarding relevant comparators in different patient subgroups
  - Treatment algorithms vary between countries
    - for patients in different treatment lines
    - for patients with different disease severity
    - dependent upon reimbursement status of therapy options

How can different HTA requirements be accommodated in this multiple sclerosis case?

- Complex subgroup analyses
  - May require larger sample sizes: Impact on development costs and time
- Indirect comparisons to demonstrate relative effectiveness versus a variety of therapy options in different patient subgroups
  - Access to comparators' data for these sub-groups may be very limited
- Extrapolation of therapeutic benefit beyond study duration and modeling to address the "lifetime horizon" in cost-effectiveness assessments
- Post-approval evidence generation in specific populations

Some general conclusions at this point in time

- Ideally, global development should integrate the requirements of regulatory and HTA agencies world-wide
- While differing regulatory requirements may be reconciled by “bridging studies”, it currently seems to be difficult to meet all specific HTA requirements from different agencies under consideration of development costs and timelines
- Despite early dialogue there remains much uncertainty, so that today HTA advice primarily helps to understand the risks linked to investment in drug development
- Any nonconformance with (country-specific) advice needs to be professionally explained, documented and tracked further on
- Disease specific, harmonized HTA guidelines for the clinical investigation of medicinal products would be very valuable
  - Pragmatic and aligned evidence requirements in specific fields
  - Study duration and endpoints appropriate for a specific disease
  - Comparators appropriate for a specific disease
  - Effect sizes considered clinically meaningful
- A disease specific set of acceptable methodologies for data analysis and synthesis might further reduce uncertainty.