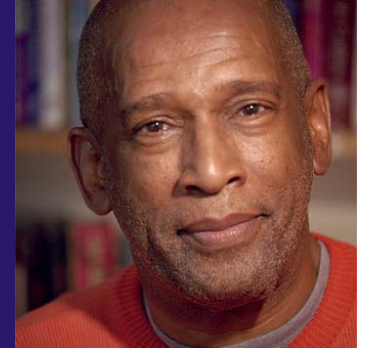


Challenge of Filing 4 New Vaccines at Once – Lessons Learned

Keith Chirgwin

Merck Research Laboratories



Lessons Learned During Recent Vaccine Filings

Outline

- Regulatory challenges with vaccines
- Managing Risk – the importance of planning
- Approach to agency feedback during development
- Managing activities during regulatory review

Background

- During 2004-2005 Merck submitted applications for marketing approval for 4 new vaccines
 - PROQUAD®
 - ROTATEQ®
 - ZOSTAVAX®
 - GARDASIL®
- Global regulatory review
 - Overlapping review cycles

Challenges in vaccine development

- Manufacturing complexity
- Integration of clinical, process and analytical development
- Relatively long development cycle
 - New information may impact development plans
- Changing regulatory environment
 - Increasing emphasis on safety

Managing Regulatory Risk

The Importance of Planning

- Planning during development
 - Identifying key regulatory issues
 - Developing a plan to address these issues
- Planning the preparation of the file
 - Well-organized dossier
 - Ensuring key label statements are supported
- Planning for activities during review
 - Pre-filing checklist
 - Challenge of global simultaneous submissions

Identifying key regulatory questions/issues

What does the efficacy evaluation need to address?

- Risk/benefit - sufficient benefit to justify use in healthy?
- Precision of estimate – lower bound
- Non-inferiority - clinically relevant equivalence margins
 - How well understood is the quantitative relationship between immunogenicity and efficacy?
 - Potential impact of decrease in efficacy on transmission

Identifying key regulatory questions/issues

What does the safety evaluation need to address?

- Risk/benefit - sufficiently safe to justify use in healthy?
- Evaluation of uncommon AEs – power to detect
 - What is a signal? Issue of multiple comparisons
- New information may change the scope/focus of the safety evaluation
 - Rotavirus vaccines and intussusception
- Questions related to new technology
 - New cell substrates – new adventitious agents
 - Novel adjuvants – cascade effects? autoimmunity?

Identifying key regulatory questions/issues

- “Non-traditional” efficacy measures
 - Novel endpoints may be less familiar
 - Need for agreement on how to measure efficacy
 - What is clinically relevant?
 - Endpoint validation
 - Surrogacy
 - How to communicate to physicians and patients

Regulatory feedback during development

- Refer to guidance when possible
- Identify questions for agency feedback
- Develop proposals for concurrence
- Some questions may require iterative discussion as data become available
- There may not be pre-defined answers to some questions
 - Potential need for broader discussion/input
- Guidance may change as science evolves

Regulatory feedback during development

- Procedural aspects
 - Formal feedback
 - US: PDUFA meetings, Special Protocol Assessment
 - EU: Scientific Advice
 - Informal feedback
 - May be particularly useful for preclinical and CMC questions which are “non-standard”
 - May be useful in helping formulate questions for Scientific Advice
 - Workload issues at agencies – being judicious with what questions to ask

Regulatory feedback during development

Examples of items for concurrence

- Clinical data supporting licensure
 - Study population
 - Safety database
 - Efficacy endpoints
 - Endpoint validation
 - Clinical assay validation
 - Criteria for success
 - Concomitant use data
 - Demonstration of manufacturing consistency

Regulatory feedback during development

Examples of items for concurrence

- Analytical Development Plans
 - Role/utility of characterization dependent on whether the product is well-characterized
 - Rationalizing analytical development plan
 - Purpose of each test, supporting data and interpretation as to why test is appropriate for chosen purpose
 - Integration of analytical, process and clinical development
 - Product specifications versus characterization
 - Comparability protocols

Managing Regulatory Risk

The Importance of Planning

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Pre-submission preparations

- Pre-submission meetings
 - Update agencies on phase III results
 - Status and timing of ongoing studies
 - Agreement on content/format of application
 - High level – not a “pre-review” of data
 - Electronic submissions considerations
 - Workload planning for agency

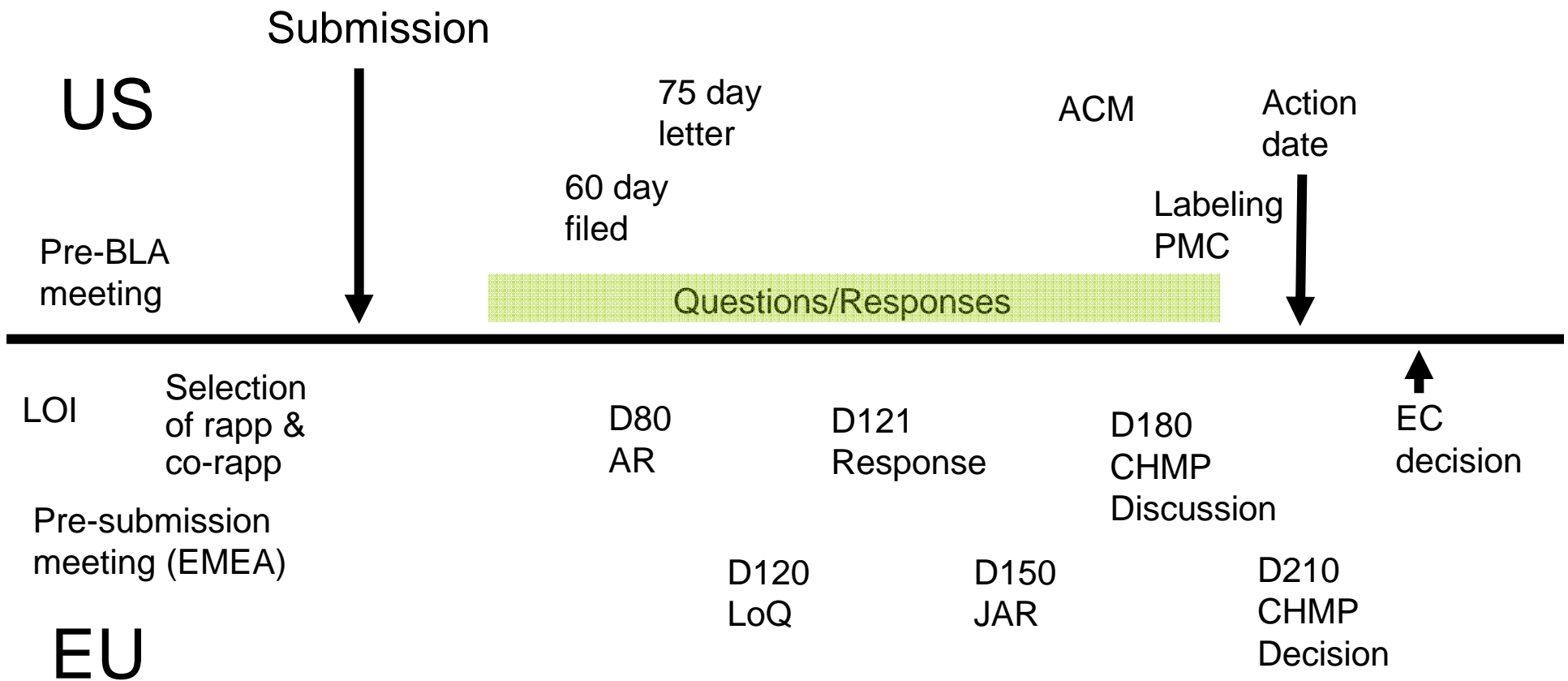
Pre-submission preparations

- Manufacturing
 - Readiness for inspections
 - Detailed review of facility information will be conducted by CBER onsite during PAI
- Batch release
 - Interactions with agencies performing batch release
 - Discussion and selection of OMCL and TOI (EU)
 - Establish release assays prior to launch

Pre-submission preparations

- Risk Management Planning
 - Early planning for post-licensure studies
 - Evaluate product use in “real-world” setting
 - Detection of less common adverse events
 - Linked databases
 - Important tool for evaluating rare AEs
 - Finite number of venues/investigators (who may have other commitments)
 - Local institutional/operational factors may impact on protocol design and timing – critical issue for PMC timing/compliance

Timeline of Review Activities in the EU and US



Advisory Committee Meetings

- Routinely convened for most new vaccines
 - Under FDAAA, FDA needs to justify not having an ACM
- External consultants asked by FDA to opine on adequacy of evidence supporting safety/efficacy
 - AC may recommend additional studies pre- or post-licensure
- Restrictive Conflict of Interest requirements
 - Challenges identifying experts without conflicts
- Need to anticipate likely questions and prepare for these

Summary/Conclusion

- Planning is key
- Use agency feedback during development to better understand the key issues for the benefit-risk evaluation
- Some questions may require a broader discussion
- New information may impact on requirements
- The environment is changing