Challenge of Filing 4 New Vaccines at Once – Lessons Learned

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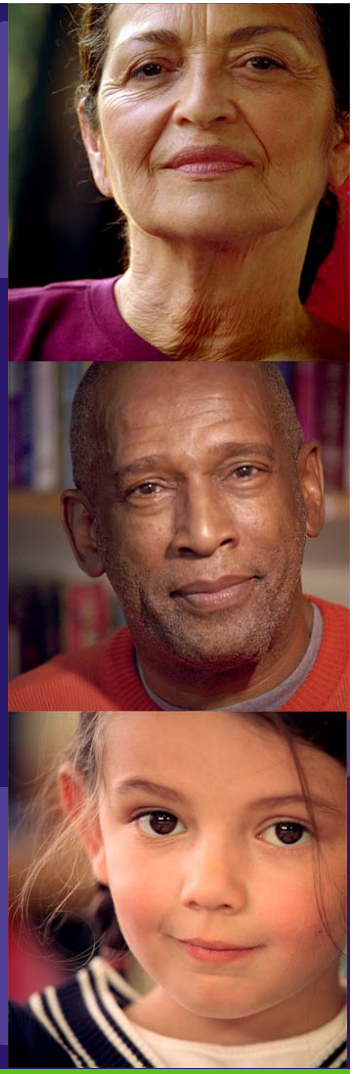

Lessons Learned During Recent Vaccine Filings

Outline

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

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Background

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

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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

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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

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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?

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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

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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

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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

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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

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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

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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

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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

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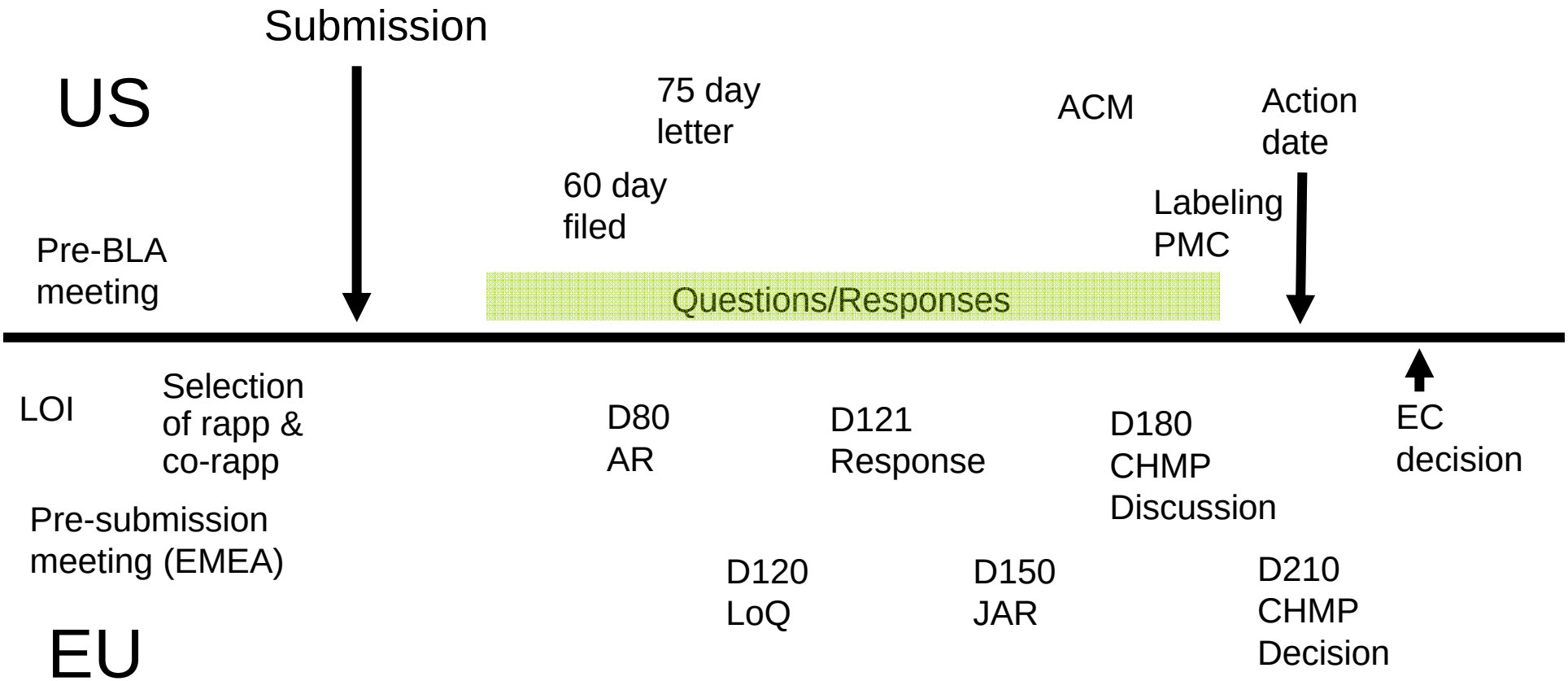
Timeline of Review Activities in the EU and US



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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

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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

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