

Phase 3 Labeling Issues

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Disclosure

- No financial relationships to disclose.

Labeling Issues

- Content
 - Highlights
 - Dosage and Administration
 - Warnings and Precautions
 - Description
 - Clinical Studies
- Format
- **How to get a label**

Stages of Drug Development

- In-vitro studies
- Preclinical animal studies
- Clinical Trials
 - Phase 1
 - Phase 2
 - Phase 3
- Marketing Approval

Meetings with OCTGT

- Standard drug development (Type B) meetings
 - Pre-preIND
 - Pre-IND
 - (End of phase 1)
 - End of phase 2
 - Pre-BLA
- Other “formal” meetings (Type A and Type C)
- Informal “meetings”

End of Phase 2 (pre-Phase 3) Meeting

- Design of Phase 3 study
- Evidence of Effectiveness
- Evidence of Safety
- Mechanism of Action

End of Phase 2 (pre-Phase 3) Meeting

- Design of Phase 3 study
 - **Special Protocol Assessment**
- Evidence of Effectiveness
- Evidence of Safety
- Mechanism of Action

Design of Phase 3 Study

- Special Protocol Assessment (SPA)
 - “having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.”
 - Designed to evaluate a specific protocol, not the overall development program.

End of Phase 2 (pre-Phase 3) Meeting

- Design of Phase 3 study
 - Special Protocol Assessment
- **Evidence of Effectiveness**
- Evidence of Safety
- Mechanism of Action

Effectiveness

- FDA Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- FDA usually requires two well-designed clinical trials, each one positive, to establish that a drug is effective.
- A single trial might provide sufficient evidence of effectiveness.

Effectiveness

FDA Guidance on Effectiveness: “Reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.”

Effectiveness

A single positive study, especially if there are multiple centers, consistency across centers, a large sample, consistency across study subsets, good rationale, multiple endpoints involving different events, and a statistically very persuasive result, may be sufficient for marketing approval.

End of Phase 2 (pre-Phase 3) Meeting

- Design of Phase 3 study
 - Special Protocol Assessment
- Evidence of Effectiveness
- **Evidence of Safety**
- Mechanism of Action

Safety Database Issues

- Size of Safety Database
 - Overall Risk-Benefit assessment
 - Considerations
 - Number and duration of administrations
 - Size of disease population
 - Adverse events seen during development
- Duration of Follow-up
 - Cell Therapy
 - Gene Therapy
- Risk Evaluation and Mitigation Strategy (REMS)
- Post-marketing Requirements (PMRs)

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- **Mechanism of Action**

Expedited Development (Fast Track)

- Drugs intended to treat life-threatening and severely debilitating illnesses, especially where no satisfactory alternatives exist
- Procedures available
 - Meetings of FDA and sponsor to plan development
 - Risk-benefit analysis considers the severity of the disease
 - Priority Review
 - Usual standards of safety and effectiveness apply
- Requires a development plan designed to show a significant improvement over available treatments

Accelerated Approval

- For serious or life-threatening diseases
- May use a surrogate endpoint which is reasonably likely to predict clinical benefit
- Requires adequate well-designed trials
- Requires meaningful therapeutic benefit over existing treatments
- Marketing approval includes a requirement of further studies to determine the true clinical benefit

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