Regulatory Considerations for NOAC Reversal Agents

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The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.
A clinician who has had to deal with perioperative and periprocedure anticoagulation and a son whose father:

is on an anticoagulant

falls a lot
Good idea

Approved drug/biologic
Good idea

Approved drug/biologic
Good idea

Approved drug/biologic
SafetY First
Preclinical

Phase 1

Phase 2

Phase 3

“Substantial Evidence of Effectiveness”
What Does the FDA Consider Substantial Evidence of Effectiveness?

• Federal Food, Drug and Cosmetic Act, 1962
  – Required effectiveness of products be demonstrated through adequate and well-controlled studies

• What qualifies as substantial evidence of effectiveness?
  – See 21 CFR 314.126 for drugs and 21 CFR 601.25 (d) (2) for biologics.
  – FDA’s “gold standard” or “classical pathway” is at least two adequate and well-controlled studies (i.e., phase 3)
  – But there could be a single such study and confirmatory data from multiple other studies.
    • Other doses and regimens, other dosage forms, other stages of disease, other populations
The FDA Amendments Act of 1997 allowed for flexibility in interpreting clinical data and for allowing a single clinical trial with adequate data to support the evidence of effectiveness.

- Large multicenter trial
- Consistency across subsets
- Statistically very persuasive findings

“It’s a matter of judgment.”

See Guidance for Industry:
Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
May 1998
NOAC Reversal Agents

• Are there potential problems with this “classical” pathway and NOAC reversal agents?
  – Small patient population
    • On NOAC
      – Have significant bleeding (2-3%)
        » Need emergent surgery/procedure
  – Feasibility
  – Adequate control
Are There Alternative Regulatory Pathways?

Good idea

Approved drug/biologic
Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

Final Guidance Published May 2014

All programs/designations are intended to address unmet medical need in the treatment of a serious condition
<table>
<thead>
<tr>
<th>Criteria (abridged)</th>
<th>Fast Track Designation</th>
<th>Breakthrough Therapy Designation</th>
<th>Accelerated Approval Pathway</th>
<th>Priority Review Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended to treat a serious condition AND Nonclinical or clinical data demonstrate the potential to address an unmet medical need</td>
<td>Intended to treat a serious condition AND Preliminary clinical evidence indicates product may demonstrate substantial improvement on a clinically significant endpoint over available therapies</td>
<td>Treats a serious condition AND Generally provides a meaningful advantage over available therapies AND Demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit</td>
<td>Treats a serious condition AND Would provide a significant improvement in safety or effectiveness OR Application or supplement submitted with a priority review voucher</td>
<td></td>
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Fast Track Designation

• Serious Condition ✓
  – Disease has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity not usually sufficient
  – Life-threatening

• Unmet medical need ✓
  – Supported early by mechanistic rationale or preclinical pharmacologic data
What Fast Track Designation Gets You

• There are opportunities for frequent interactions with FDA. These include meetings, including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers.

• **Rolling Review** - reviewing portions of a marketing application before the sponsor submits the complete application
Breakthrough Therapy Designation

- Serious Condition ✔
- Preliminary clinical evidence demonstrate substantial improvement on a clinically significant endpoint
  - Is a laboratory test alone a clinically significant endpoint?
What Breakthrough Therapy Designation Gets You

• Intensive FDA guidance as early as phase 1
• Intensive involvement of senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review
• Rolling Review
• Possibility for Priority Review
Accelerated Approval Pathway

• When “routine” clinical studies are impractical or unethical (e.g. mortality with slow growing tumor or with rare clinical events)

• Requires the same statutory standards for safety and efficacy as a routine application

• A surrogate endpoint – or an intermediate clinical endpoint – likely to predict clinical benefit
  – There is precedent for using laboratory data as surrogate (Factor Xa reversal agent)

• Postmarketing confirmatory trials are required to verify and describe the anticipated effect on surrogate or intermediate clinical endpoint or other clinical benefit
Accelerated Approval Pathway

- Serious Condition ✓
- Meaningful advantage over available therapy ✓
- Effect on endpoint that is reasonably likely to predict clinical benefit
  - Clinical data should be provided to support a conclusion that a relationship of an effect on the surrogate endpoint or intermediate clinical endpoint relates to an effect on the clinical outcome and is reasonably likely.

- Confirmatory trial(s) should directly measure clinical benefit and be underway at the time of submission of original application
Use of a Surrogate Endpoint

• Understand the disease process ✔

• Understand the relationship between the drug’s effect and the disease process ✔
What Accelerated Approval Gets You

• Earlier approval of product based on a surrogate rather than a direct clinical endpoint
• -BUT- use of a surrogate requires post marketing clinical trials to validate the surrogate marker.
• Failure to validate the surrogate after approval may lead to withdrawal of FDA approval for that product.
Priority Review Designation

• Treats a serious condition and would provide a significant improvement in safety and effectiveness of the treatment, prevention, or diagnosis of a serious condition.

• Products under Fast Track Designation, Breakthrough Designation or Accelerated Approval Pathway are also eligible for Priority Review Designation.
What Priority Review Designation Gets You

• Shorter clock for review of a marketing application (8 months versus 12 months in PDUFA V)
Summary

• Generally one to two adequate and well-controlled clinical studies are required to establish safety and efficacy for new products

• Expedited programs are available for products intended for serious and life threatening diseases with unmet medical needs

• These programs are defined and these criteria are readily available in a recently published FDA Guidance.
Resources

• FDA Guidances
  – Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

• Questions and Answers about the Expedited programs can be found at:
  http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm341027.htm