Regulatory Flexibility and Lessons Learned: Drugs for Rare Diseases

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Disclosures

• No Conflicts of Interest
• Nothing to Report
• Opinions expressed are personal and do not reflect those of the FDA
Statutory Requirements for new drug approval:

• Substantial evidence of effectiveness for treatment of the proposed indication
• Benefits for proposed population outweigh risks
• Manufacturing that ensures product identity, strength, quality (purity)
• Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively
Substantial Evidence of Effectiveness

• Demonstration of substantial evidence of effectiveness requires studies designed well enough “to distinguish the effect of a drug from other influences, such as spontaneous change… placebo effect, or biased observation”

• Usual approval standard is two adequate and well-controlled studies

21CFR 314.50 and 21CFR 314.126
A Problem?

Can drug development programs for rare diseases meet the same approval standards as programs for diseases with millions of potential trial participants?
Solution: Flexibility Is Part of FDA Regulations

- Regulations allow for flexibility and judgment in applying the standards
- FDA has a solid record of appropriately applying regulatory flexibility

21 CFR 314 (APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG)
Flexibility

“While the statutory standards apply to all drugs... the many kinds of drugs... and wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.”
How Much Evidence Is Enough?

FDA may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence.
Flexibility in FDA regulations does not mean marketing approval prior to demonstration of substantial evidence of effectiveness
## Application of Flexible Clinical Development Programs
### CDER NME approvals 1/1/2008 – 9/25/2015

<table>
<thead>
<tr>
<th>Flexible Development Programs</th>
<th>Rare Approvals</th>
<th>Non-Rare Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ≥ 1 flexible development approaches*</td>
<td>81%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>N=73</td>
<td>N=64</td>
</tr>
<tr>
<td>Traditional development program**</td>
<td>19%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>N=17</td>
<td>N=113</td>
</tr>
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*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥2 AWC studies using endpoints with prior precedents
Programs to Expedite Drug Development

• Fast Track Designation
  – FDAMA 1997/FDASIA 2012

• Breakthrough Therapy Designation
  – FD&C Act/FDASIA 2012

• Priority Review
  – PDUFA 1992

• Accelerated Approval
## Expedited Clinical Development Programs

**CDER NME approvals 2008-2016***

<table>
<thead>
<tr>
<th>Expedited Programs</th>
<th>Number Rare (n = 109)</th>
<th>Number Non-Rare (n = 193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review</td>
<td>75%</td>
<td>30%</td>
</tr>
<tr>
<td>Fast Track</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>26%</td>
<td>2%</td>
</tr>
<tr>
<td>Breakthrough Therapy**</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>Used any Expedited Program</td>
<td>86%</td>
<td>35%</td>
</tr>
</tbody>
</table>

*as of September 7, 2016, **BT initiated 2012
Highlights of Recent Novel New Drug Approvals
October 2015 – 03 October 2016

• 17 Approvals for Rare Disease Indications
  – 10 for oncology indications

• 7 BLAs and 10 NDAs

• 8 Designated as Breakthrough Therapy

• 2 Received a Rare Pediatric Disease Priority Review Voucher
Highlights of Recent Novel New Drug Approvals
October 2015 – 03 October 2016 (cont.)

• 6 Received Accelerated Approval
  – 4 for oncology Indications
• 1 Employed a novel End Point
• 12 Approved with fewer than 2 Adequate and Well Controlled Trials
Understanding FDA Pathways to Drug Approval
There are TWO Approval Pathways in the US

Traditional (regular or “full”) Approval and Accelerated Approval

the statutory standards are the same for both
demonstration of substantial evidence based on adequate and well-controlled clinical study(ies)
• **Accelerated approval** is **not** about faster review - it is a **regulatory pathway** to speed availability of drugs for serious unmet need by using an appropriate, *more readily measured, surrogate or intermediate clinical endpoint* when a lengthy trial would be needed to measure direct clinical benefit of a drug.
Accelerated Approval

• The candidate drug must provide a meaningful advantage over available therapies to treat a serious condition, generally irreversible morbidity or mortality

• Relies on a more readily measured surrogate or intermediate clinical endpoint

• A post-approval confirmatory study to further define clinical benefit is generally required
Clinical vs. Surrogate Endpoints

• **Clinical** endpoint: characteristic or variable that *directly* measures a therapeutic effect - how a patient feels, functions, or survives

• **Surrogate** endpoint for accelerated approval: marker *thought reasonably likely to predict* clinical benefit; not itself a measure of benefit
Lessons learned from eteplirsen and other recent rare disease programs
• A poorly planned and executed development program for a rare disease misuses valuable patient resources and serves to delay obtaining the knowledge required to understand the benefits and risks of a drug to support regulatory review and approval

• FDA provides valuable advice and guidance to sponsors, we cannot require sponsors to follow our advice

• Path taken by Sarepta NOT a good model for other development programs
• Assays for biomarkers should be well validated before use to avoid obtaining misleading information and wasting clinical specimens
  • Particularly true when invasive procedure required to collect tissue in children
• Rigorous blinding and control procedures should be in place to minimize bias in assay interpretation
  • Protocol should specify blinding procedures, adjudication methods, independence of readers, etc.
• In many cases, randomized controlled clinical trials represent the fastest way to determine if a drug is effective
• Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials
• Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)
• Report early trial results accurately, post hoc analyses of failed trials are generally hypothesis generating for next trial, not evidence to support approval
• Knowledge of natural history of disease is critical to intelligent design of clinical trials
  • Conduct natural history trials before clinical trials begin
• If a natural history external control group is proposed, it should be identified prospectively to ensure comparability to treatment group
  • Natural history external control group created post hoc is very difficult to interpret, unless effect of test drug is very large, due to known and unknown confounding
• Use of accelerated approval pathway should be prospectively planned, **NOT** as a “rescue” for a failed program

  • Sponsor and FDA should agree on the surrogate and drug effect considered “reasonably likely” to predict clinical benefit **before** unblinding data

  • “Any” effect of a drug on a biomarker is not a basis for AA

  • Ideally, the confirmatory trial to further define clinical benefit should be started before AA is granted to ensure the trial will be completed in a timely manner
FDA welcomes the engagement of patients and caregivers in helping to design development programs that will result in drugs that provide meaningful clinical benefit to those with disease.

Approval decisions must be based on data from adequate and well-controlled clinical trials, which may include PROs and other patient-derived measures.

Experience of patients enrolled in trials can be very helpful; discordant results between trial data and patient anecdotes are very hard to reconcile.
• FDA reviewers are committed to facilitating development of effective and safe drugs for rare diseases

• Upholding statutory standards for approval in face of hopes and desires of patients, families, sponsors, and investors is a very difficult job

• Personal attacks on FDA reviewers creates an atmosphere of distrust and isolation rather than collaboration

• Recruitment and retention of qualified review staff is very challenging in such an environment
Thank you very much for your attention!

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CDER/FDA