Quantum of Effectiveness
Evidence in FDA’s Approval of Orphan Drugs

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Quantum of Evidence Required

- Efficacy evidence required under the FD&C Act
  - “Substantial evidence” of effectiveness
  - “Adequate and well-controlled investigations”

- Orphan Drug Act of 1983
  - Did not change the quantum or quality of either the safety or effectiveness evidence needed for drugs intended for rare disorders
Formal FDA Policies and Statements

- FDA has regulations and policies providing greater flexibility for certain types of drugs (e.g., Subpart H), or under certain circumstances (e.g., May 1998 Evidence Guidance).

- FDA has publicly recognized its exercise of flexibility specifically for drugs treating Americans with rare diseases (e.g., Dr. Griebel’s statement at Jan. 13, 2010 Carbaglu [#31] advisory committee meeting; Dr. Katz’s statement at this conference last October on Xenazine [#122] as approved under FDAMA 115).
FDA Policy on Orphan Drugs

- At June 29, 2010 first FDA hearing on orphan drugs, NORD requested that FDA issue a policy statement on its regulation of orphan drugs, to among other objectives,
  - explain FDA’s exercise of scientific discretion in flexibly applying statutory standards for establishing efficacy

- NORD recognized the difficulty in developing such a policy “given that each investigational therapy for a rare disorder will present unique features”.

- NORD, however, asked that, at a minimum, “even cataloguing the nature and scope of the orphan drug precedents that illustrate FDA’s flexibility may enable key stakeholders to better understand FDA’s position”. 
Cataloguing FDA’s Orphan Drug Actions

To facilitate the requested action, NORD embarked on this analysis in order

- To examine whether FDA exercises flexibility when reviewing applications for orphan diseases, and
- If so, to illustrate the nature and scope of that flexibility
Methods

- Scope of analysis: all 135 orphan drug new chemical entities approved from 1983 to June 30, 2010 (excluding those for rare cancers)

- For each of the 135 drugs:
  - Reviewed FDA’s publicly-available documents (totaling 27 boxes, primarily medical and statistical reviews)
  - Classified the level of “efficacy evidence” determined by FDA to be adequate for drug approval

- Review & classification done by author experienced in orphan drugs*

- Author’s analysis of 1983 law while at FDA led to 1984 and 1985 amendments, and, since leaving FDA in 1987 author has been working with FDA, drug sponsors, researchers and patient advocates on orphan therapies, including key contributions on 30 of the 135 drugs in this analysis.
Classes of Efficacy Evidence

1. “Conventional”
   - Evidence would satisfy the two adequate and well-controlled studies standard

2. “Administrative Flexibility”—formal FDA policy
   - FDAMA 115
   - Subpart H of 21 C.F.R. Part 314 (accelerated approval, Fast Track)
   - Subpart E of 21 C.F.R. Part 312

3. “Case-by-Case Flexibility”
   - For each of the 58 drugs in this class, an explanation is provided since each has some unique feature
“126. Treprostinil sodium - Remodulin

This May 2002 approval to treat pulmonary arterial hypertension was based on the results of two concurrently run, identically designed trials, both of which were double-blind, randomized, placebo-controlled with a primary endpoint of the 6 minute walk test of exercise capacity. The sponsor and FDA had agreed in advance that a positive result would be either: (a) both trials having a p value of < 0.05 on the primary endpoint; or (b) one trial having a p of <0.05 plus the pooled result having a p value of < 0.01. The primary endpoint results of each of the two trials were p values of 0.0607 and 0.0550, while the pooled result was 0.0064.”
## Results: FIGURE 1

<table>
<thead>
<tr>
<th>Chemical and Brand Names</th>
<th>Approval (mm/yy)</th>
<th>Conventional Flexibility</th>
<th>Administrative Flexibility</th>
<th>Case-by-case Flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1    Agalsidase betal</td>
<td>04/2003</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2    Albendazole – Albenza</td>
<td>06/1996</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3    Alglucerase – Ceredase</td>
<td>04/1991</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>134  Zidovudine – Retrovir</td>
<td>03/1987</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>135  Zoledronic Acid – Zometa</td>
<td>08/2001</td>
<td>X</td>
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**Sub Totals:**

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<tbody>
<tr>
<td></td>
<td>45</td>
<td>32</td>
<td>58</td>
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**Flexibility:**

- Not Needed: 45
- Yes: 90
## Stability of Flexibility

### Analysis of Efficacy Evidence by Decade

<table>
<thead>
<tr>
<th>Orphan Drug Efficacy Evidence</th>
<th>Conventional</th>
<th>Total Flexibility</th>
<th>Administrative Flexibility</th>
<th>Case-by-case Flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period</td>
<td></td>
<td></td>
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<tr>
<td>1980 – 1989</td>
<td>7 (33.3%)</td>
<td>14 (66.7%)</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>1990 – 1999</td>
<td>21 (35.6%)</td>
<td>38 (64.4%)</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>2000 – 2010</td>
<td>17 (30.9%)</td>
<td>38 (69.1%)</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>90</td>
<td>32</td>
<td>58</td>
</tr>
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</table>
RESULTS

- 90 of the 135 orphan drug approvals or 67% resulted from some exercise of FDA flexibility in applying the statutory standard for evidence of effectiveness.
Conclusions

- Historically FDA has regularly exercised regulatory flexibility in approving therapies for Americans with rare diseases.
- NORD hopes that this analysis will aid FDA in developing and issuing a formal policy statement on FDA’s regulation of therapies for persons with rare diseases.
- NORD also hopes that this effort by NORD will crystallize for rare disease patient advocates, academic researchers, pharmaceutical companies (engaged in orphan therapy development) and the financial community the nature, scope and extent to which FDA has exercised its scientific discretion in regulating therapies for those with rare disorders.
Thank you!

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