Rare Diseases Drug Development and Patient Perspective Initiatives at FDA

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Improving the Clinical development Process
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Disclosures

• No Conflicts of Interest
• Nothing to Report
• Opinions expressed are personal and do not reflect those of the FDA
CDER Rare Diseases Program

Mission Statement:
• Facilitate
• Support
• Accelerate

…the development of drug and biologic products for the treatment of patients with rare disorders
Rare Diseases Program Projects (I)

Coordinate development of CDER Policies, Procedures and Training

• Several guidances under development
• Continuing involvement with Senior FDA staff re: Rare Diseases Program
• Review Rare Pediatric PRV requests and developed procedures for review and administration

Assist in development of good science

• Regulatory database adjudication committee for NMEs
• Specific projects/peer reviewed publications
Rare Diseases Program Projects (II)

Work collaboratively with stakeholders

- NIH Collaborations
  - NIH/FDA Joint Task Force
  - Rare Disease Day Annual Meeting
  - CDER/TRND Drug Development Meetings

- Patient/Patient Organizations Meetings
  - Panel Participation in FDA Patient Focused Drug Development Workshops
  - Face to Face meetings with patient advocacy groups often in collaboration with PASE and/or OHCA
  - Presentations to stakeholder groups
  - Planning Committee members for NORD Annual Summit

- FDA Rare Disease Council member
- Respond to queries from internal and external stakeholders
- Working Group member of FDASIA Section 1137 – “Patient Participation in Medical Product Discussion”
Rare Diseases Program Projects (III)

Promote consistency and innovation in review

• Annual Rare Diseases Training Course for FDA Review staff
• CY 2015 to date, attended >100 pre-IND, EOP2, and pre-NDA review division meetings for rare diseases
• Presentations to numerous professional societies
Regulatory Approaches and Programs Benefiting Rare Diseases

Clinical Development

• Review flexibility
• Expedited programs for serious conditions
Drug Approval Standards

• The standard for approval of rare disease drugs and biological products is the same as for prevalent disease drugs - substantial evidence of product effectiveness.

• “Substantial evidence” is defined as: “evidence consisting of adequate and well-controlled (A&WC) investigations… on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use…”

Kefauver Harris Amendment –FD&C Act § 505(d), 21 USC 355(d) (1962)
See Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998
Flexibility

• The regulations do, however, allow for **flexibility** and **scientific judgment** in applying the standard, and in determining the kind and quantity of data required to be provided for a particular drug

• For rare disease drugs, relying on one A&WC trial with supporting evidence is not unusual, but the adequacy of this approach for any given drug must be considered in the context of the disease, the population, the properties of the drug, and the magnitude of the clinical trial results

Kefauver Harris Amendment -FD&C Act § 505(d), 21 USC 355(d) (1962)
As amended by Food and Drug Administration Modernization Act Sec 115 (1997)
Flexibility

- Reliance on a single A&WC study* is generally 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, in which case confirmation of the result in a second trial would be practically or ethically impossible.

- However, other considerations apply for serious rare diseases with unmet medical need and it is critically important to consider proposals for relying on a single trial early in planning within the context of the entire clinical development plan.

*Described at 21 CFR 314.126
### Application of Flexible Clinical Development Programs for Rare Diseases

**CDER NME approvals 2008-2014 - Exploratory Analysis**

<table>
<thead>
<tr>
<th>Flexible Development Programs</th>
<th>Rare Disease Approvals</th>
<th>Prevalent Disease Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ≥ 1 flexible development approaches*</td>
<td>65 (80%)</td>
<td>49 (32%)</td>
</tr>
<tr>
<td>Traditional development program**</td>
<td>16 (20%)</td>
<td>103 (68%)</td>
</tr>
</tbody>
</table>

*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 precedence
Expediting Rare Diseases Drug Development

• Fast Track
  – FDAMA 1997/FDASIA 2012

• Breakthrough Designation
  – FD&C Act/FDASIA 2012

• Priority Review
  – PDUFA 1992

• Accelerated Approval

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
Use of Expedited Clinical Development Programs for Rare Diseases
CDER NME approvals 2008-2014 – Exploratory Analysis

<table>
<thead>
<tr>
<th>Expedited Programs</th>
<th>Rare Disease Approvals (n = 81)</th>
<th>Prevalent Disease Approvals (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review</td>
<td>60 (74%)</td>
<td>43 (28%)</td>
</tr>
<tr>
<td>Fast Track</td>
<td>48 (59%)</td>
<td>33 (22%)</td>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>21 (26%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Breakthrough Therapy</td>
<td>9 (11%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Any Expedited Program</td>
<td>69 (85%)</td>
<td>51 (34%)</td>
</tr>
</tbody>
</table>
Rare Diseases: Common Issues in Drug Development (Draft) Guidance for Industry/August 2015

• Adequate description and understanding of the disease’s natural history
• Adequate understanding of the pathophysiology of the disease and the drug’s proposed mechanism of action
• Nonclinical pharmacotoxicology considerations to support the proposed clinical investigation(s)
• Reliable endpoints and outcome assessment
• Standard of evidence to establish safety and effectiveness
• Drug manufacturing considerations

Office of Health and Constituent Affairs (OHCA)

• Serves as the central point of communication and education about the FDA’s public health and regulatory activity...

• Advises the Commissioner…on … programs and initiatives that affect external stakeholder groups....

• Serves as a Liaison between FDA and…patient advocacy organizations to solve problems and address concerns…with agency policies and programs related to human and medical product development and safety
Office of Health and Constituent Affairs (OHCA)

• Patient Representative Program
  • Helps to capture the unique perspective of patients and family members directly affected by a serious life-threatening disease
  • Serve as SGEs (Special Government Employees) at advisory committee meetings to review products and policies related to serious and life-threatening diseases
  • Participate in other FDA-related activities where the patient perspective is needed

• FDA Patient Network
  • Newsletter, Webpages, Annual Meeting
Professional Affairs and Stakeholder Engagement (PASE) CDER/FDA

• Provides leadership and direction for developing, communicating, implementing, and assessing an advocacy and stakeholder relations strategy for CDER
• Conducts research to ensure that CDER has a thorough understanding of partner, stakeholder, and public opinion
• Manages and coordinates preventable harm and/or safe medication use projects across the FDA, federal agencies, and other private and public sector stakeholders
Clinical Outcome Assessment Qualification Program
A Drug Development Tool (DDT) Qualification Program*

• Clinical outcome assessments (COAs) measure:
  • a patient’s symptoms
  • overall mental state
  • or how the patient functions in daily life

• COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit.


Biomarker Qualification Program
A Drug Development Tool (DDT) Qualification Program*

• Provides a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
• Facilitates integration of qualified biomarkers in the regulatory review process
• Encourages the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
• Supports outreach to relevant external stakeholders to foster biomarker development

Thank you very much for your attention!

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