CDER 2016 Update for Rare Diseases

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CDER, FDA
Challenges for Rare Disease Drug Development

- Rare diseases natural history is often poorly understood/characterized.
- Diseases tend to be progressive, serious, life-limiting and life-threatening and lack approved therapy.
- Small populations often restrict study design and replication and use of usual inferential statistics.
- Phenotypic diversity within a disorder adds to complexity, as do genetic subsets.
- Well defined and validated endpoints, outcome measures/tools, and biomarkers are often lacking.
- Lack of precedent for drug development.
- Ethical considerations for children in clinical trials.

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Predicting the Future of Rare Disease Drug Development: Orphan Designation Applications

<table>
<thead>
<tr>
<th>Period</th>
<th>Average # Received</th>
<th>Average # Designated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983-2001</td>
<td>82</td>
<td>59</td>
</tr>
<tr>
<td>2002-2008</td>
<td>173</td>
<td>119</td>
</tr>
<tr>
<td>2009-2016</td>
<td>374</td>
<td>248</td>
</tr>
</tbody>
</table>
• Orphan Drug Approvals now greater than 40% of approvals for new molecular entities in 2015 and 2016.
CDER Novel Orphan Drug Approvals CY 2014 -2016*

* as of 31 December 2016
Expediting Rare Diseases Drug Development

• Programs have been developed to target serious diseases with unmet medical needs when a new treatment could provide meaningful clinical benefit

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
CDER Ensures That Novel Drugs Receive Expedited Review

- 73% of new drug approvals in 2016 used an expedited pathway
  - More than half (68%) of the novel drugs approved to date in CY15 were approved under **Priority Review**
  - About one-third (36%) of novel drugs approved to date in CY15 received **Fast Track** designation
  - 27% were **Accelerated Approvals**
  - 32% were **Breakthrough** designated products
Evaluation of Breakthrough Therapy Designation Program

• Pace of submissions and designations continues strong

• Evaluation as of December 31, 2016
  – Received 412 requests for breakthrough therapy designation
  – CDER granted 144: Hem Onc and antivirals lead but orphan diseases also common
  – 59 original/supplemental applications approved
  – 199 denied, 8 rescinded
Impact of Breakthrough Designation

• Friends of Cancer Research
  – Review time approximately 3 months faster
  – Development time 2.2 years less
  – Greater use of phase 1:2 data
  – Greater use of accelerated approval

• FDA internal analyses
  – Approximately 3 years less development time
  – Review times about 1-2 months less
# Expedited Clinical Development Programs
## CDER NME approvals 2008-2016

<table>
<thead>
<tr>
<th>Expedited Programs</th>
<th>Number Rare (n = 113)</th>
<th>Number Non-Rare (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review</td>
<td>87 (77%)</td>
<td>59 (30%)</td>
</tr>
<tr>
<td>Fast Track</td>
<td>62 (55%)</td>
<td>43 (22%)</td>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>31 (27%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Breakthrough Therapy</td>
<td>22 (19%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Used any Expedited Program</td>
<td>98 (87%)</td>
<td>69 (35%)</td>
</tr>
</tbody>
</table>
# Expedited Clinical Development Programs

**CDER NME approvals 2008-2016**

<table>
<thead>
<tr>
<th>EXPEDITED PROGRAMS</th>
<th>Breakthrough N=30</th>
<th>Fast Track N=105</th>
<th>Priority N=146</th>
<th>Accelerated Approval N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARE (N = 113)</td>
<td>19%</td>
<td>55%</td>
<td>77%</td>
<td>27%</td>
</tr>
<tr>
<td>Oncology</td>
<td>28%</td>
<td>58%</td>
<td>84%</td>
<td>48%</td>
</tr>
<tr>
<td>Non-Oncology</td>
<td>13%</td>
<td>52%</td>
<td>71%</td>
<td>11%</td>
</tr>
<tr>
<td>NON-RARE (N = 195)</td>
<td>4%</td>
<td>22%</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>Oncology</td>
<td>11%</td>
<td>42%</td>
<td>68%</td>
<td>11%</td>
</tr>
<tr>
<td>Non-Oncology</td>
<td>3%</td>
<td>20%</td>
<td>26%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Application of Flexible Clinical Development Programs
CDER NME approvals 2008-2016

<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>88 (78%)</td>
<td>68 (35%)</td>
</tr>
<tr>
<td>Traditional development program**</td>
<td>25 (22%)</td>
<td>127 (65%)</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 precedents
### Flexible Clinical Development Programs

CDER NME approvals 2008-2016

<table>
<thead>
<tr>
<th>NOVEL ENDPOINTS</th>
<th>Yes N=38</th>
<th>No N=270</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARE, n=113</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>Oncology</td>
<td>2%</td>
<td>98%</td>
</tr>
<tr>
<td>Non-Oncology</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>NON-RARE, N=195</td>
<td>7%</td>
<td>93%</td>
</tr>
<tr>
<td>Oncology</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Non-Oncology</td>
<td>7%</td>
<td>93%</td>
</tr>
</tbody>
</table>
“Patient-focused” Drug Development

• We understand that people with chronic diseases are “experts” in that disease, as far as the symptoms and the impact on QOL, and what might be acceptable tradeoffs
  – On risk
  – On uncertainty
• Have had >20 of 24 PFDD meetings, more to go, reports generated
• How to meaningfully collect that knowledge, in rigorous manner, given that there is a spectrum of opinions and a spectrum of disease burden in any given disease?
• How to do this for the many thousands of diseases?
• Working with multiple patient organizations who are pioneering patient-focused guidance development for their disease of focus
Expanded Access Programs at FDA

• Use of an investigational drug or biologic to treat a patient with a serious or immediately life threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
  • For an investigational drug in a clinical trial, the primary intent is research

• There are three types of access:
  • Individual patients (21CFR312.310)
  • Intermediate size population (21CFR312.315)
  • Treatment IND (21 CFR312.320)

Expanded Access Programs at FDA

Submissions and Protocols
• Of 7291 submissions and Protocols from FY 2010 - 2015
  • 99.5% were allowed to proceed
  • 97.3% of expanded access submissions were for single patient protocols or single patient emergency protocols

Safeguards for Participants
• Informed consent
• IRB review
• Reporting requirements

http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm443572.htm
Expanded Access: Improving the Regulatory Process

• Adverse events in EA do not derail clinical development
  – In 10,000 INDs only 2 temporary clinical holds due EA AE
• Laborious and somewhat complex process in past.
• This year new simplified form (3926)
  – Estimated time 45 minutes
• 3 new Guidances,
  – Questions and Answers; Charging for Investigational Drugs Under an IND;
  – Individual Patient Expanded Access Applications: Form FDA 3926 final guidance
• Navigating a complex landscape in expanded access
Targeted Therapies

• Targeted therapies have grown from 5% of new drug approvals in the 1990s to 45% in 2013.
  – 80% of breakthrough designations and about 44% of recently approved orphan products

• Common disease subsets \(\square\)“orphan subsets”\(^1\)
  – E.g., BRAF V600 mutation subsets of melanoma

• Rare Diseases and Rare Disease subsets
  – E.g., Cystic Fibrosis G551D mutation subset

• Smaller subsets available for clinical trials, smaller clinical development programs
  – Larger magnitude of effects anticipated
  – Safety, R-B assessments
Targeted APs Trending Up Over Time

CDER Targeted Therapy NME/BLA Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Targeted Therapies, % of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>1990-1992</td>
<td>~8%</td>
</tr>
<tr>
<td>2000-2002</td>
<td>~10%</td>
</tr>
<tr>
<td>2010-2014</td>
<td>~25%</td>
</tr>
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</table>
Rare Diseases Program in CDER

– Established in 2010
  • Located within the Center for Drug Evaluation and Research (CDER) in the Office of New Drugs (OND) Immediate Office
  • Associate Director for Rare Diseases (ADRD) was the first position created
– Reports to Director of the Office of New Drugs
– Staffing
Rare Diseases Program Projects

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 Disease Priority Review Voucher 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: Common Issues in Drug Development
August 2015 (Draft Guidance)

• To assist sponsors of drug and biological products intended to treat or prevent rare diseases
• To help sponsors conduct more efficient and successful development programs

Rare Pediatric Disease (RPD) Priority Review Voucher Program

• 2012 FDA Safety and Innovation Act (FDASIA) [Section 908]
  • Provides an incentive to encourage the development of drugs and biologics for rare pediatric diseases

• Upon approval, the sponsor may be issued a voucher redeemable for a priority review for a subsequent application that may not have otherwise qualified for a priority review

• The incentive offers a shorter review clock for marketing applications, 6 months compared with the 10 months standard review time

Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry
RPD Requests and Determinations

Data as of September 15, 2016
Rare Pediatric Disease Priority Review Voucher Program

• The OOPD reviews requests for Rare Pediatric Disease designation
  • 41 Designated/6 Denied/7 Under Review

• Voucher requests are managed by the OND RDP
  • 11 Voucher requests were submitted with an NDA or BLA
    • 7 Vouchers awarded, 3 denied and 1 pending review
  • Two PRV’s have been redeemed

• Future (?)
  • Sunsets - 30 September 2016 although pending legislation may be extended to 31 December 2022 (for designation)/31 December 2027 (for redemption)
Regulatory Collaborations

• Enhanced international collaborations in recent years
• EU:
  – International Rare Disease research Consortium (IRDIRC)
    • Several FDA members participate
  – Harmonized orphan drug designation application form
  – Regular meetings on orphan drugs, cancer, and pediatrics
  – New Rare Disease Cluster with EMA

• NIH
  – CDER-NIH CC taskforce
  – IND regulatory training workshop
How Does FDA “view orphan diseases”

• Is the bar different for efficacy?
  – Yes and no, standards must be present to demonstrate the drug is safe and efficacious in adequate and well controlled trials but the agency has demonstrated tremendous flexibility.

• Functional vs “hard” (survival) endpoints
  – Both acceptable if clinically meaningful and a difference is clearly demonstrable due to therapy. Intermediate clinical endpoints can be used in accelerated approvals as well as qualified surrogate markers likely to predict clinical benefit.

• Label “expansion” when the disease has different subpopulations
  – It depends but open to broad label under some circumstances.

• Can natural history be used as a control
  – Yes, if collected rigorously in a truly comparable population with a well demarcated endpoint or “hard” endpoint and a major undeniable difference is identified.
Important Lessons Learned in Rare Disease Drug Development

• Early natural history studies are invaluable
  – Best if protocol driven, rigorous, consistent objective endpoints

• Better translational development
  – Biomarker assays SHOULD be qualified before clinical studies begin if they are to be seriously considered.

• Need to consider randomization and placebo controls from the very beginning of clinical studies when equipoise clearly exists
Summary

• More therapies for Orphan diseases approved in 2015 than ever before, a strong trend continues (47% (n=21))
• Drug Development for Orphan diseases uses expedited review to a great degree
• Targeted Medicines are increasing and are common among therapies for Orphan diseases with both advantages and challenges
• Patient centered drug development is important in orphan disease
• FDA is willing to be very flexible in its approach to serious rare diseases with unmet need
• Recent experience has taught us very valuable lessons regarding natural history, early robust assay development, and randomization from the beginning of clinical studies
• Rare disease voucher can be valuable incentives
• There is an increased level of global collaboration on rare diseases