The State of Rare Disease Drug Development: An FDA Perspective

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Current Priorities at CDER

- **FDASIA**
  - Expedited reviews and Breakthrough
  - Rare diseases
  - Antibiotic development
  - Drug shortage
  - GDUFA goals
  - Electronic submissions

- **Patient Centered Drug Development**
- New Legislation ie Pharmacy Compounding/Track and Trace
- **Rethinking Pharmaceutical Quality**
- Improve Drug Labels
- Drug Safety: Sentinel/IMEDS
- PDUFA V goals
- Build an IT infrastructure that will support these goals
2013 Continues A Strong Track Record For Drug Innovation In The U.S.

- More than a third (36%) of novel drugs approved to date in CY13 are for rare diseases

- Nearly one out of three (32%) of novel drugs approved to date in CY13 are the first in their class

- Approximately three-quarters (72%) of novel drugs approved to date in CY13 were first approved in the U.S.
CDER: Rare Disease Novel Product History

- CY2008-2013* (*as of December 6, 2013)
  - Rare diseases ~1/3 of NME and original biologic APs at CDER
CDER: Expedited Programs

• Rare Diseases
  - Most are serious or life-threatening, unmet medical needs
  - Most qualify for at least one expedited program
    • Many qualify for >1 (almost all for incentives)
    • Rare>>common diseases for expedited programs
Targeted Therapies

- Considered targeted therapy if patients identified for inclusion/exclusion in pivotal trials or for drug use in labeled indication based on a genetic test, biomarker or susceptibility test (e.g., bacterial resistance, tumor genetic mutation)
- Recent analysis of approved NMES and original biological products from 2010-2013, n=121

**CDER NME/BLA Approvals 2010-2013***

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<th>Targeted</th>
<th>Non-Targeted</th>
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<td>Rare, n=42 (%)</td>
<td>23 (55)</td>
<td>19 (45)</td>
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<td>Common, n=79 (%)</td>
<td>11 (14)</td>
<td>68 (86)</td>
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<td>Total, n=121 (%)</td>
<td>34 (28)</td>
<td>87 (72)</td>
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*As of December 6, 2013
## Targeted APs Increasing Over Time

### CDER Targeted Therapy NME/BLA Approvals

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<th>Year</th>
<th>Targeted Therapies, % of Total</th>
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<td>All</td>
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<td>1990-1992</td>
<td>~8%</td>
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<td>~10%</td>
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<td>2010-2012</td>
<td>~25%</td>
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<td>2013*</td>
<td>~45%</td>
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*Jan 1-Dec 6, 2013*
CDER Pays Attention That Novel Drugs Receive Expedited Review

- 9 out of 25 (36%) novel drugs approved to date in CY13 were approved under Priority Review
- 9 out of 25 (36%) novel drugs approved to date in CY13 received Fast Track designation
Expedited Review

• Draft guidance recently provided for expedited approvals addressing serious diseases with unmet needs (June ‘13)
  – Fast track
  – Accelerated Approval
  – Priority Review
  – Breakthrough
  • New designation established by FDASIA that expedites the development and review of drugs that—
    • treat serious/life-threatening disease; and
    • preliminary clinical evidence indicates that drug may demonstrate substantial improvement over existing therapies on ≥ 1 clinically significant endpoints
Breakthrough therapy

- Features of breakthrough therapy designation include:
  - Frequent FDA/sponsor communications & meetings
  - Cross-disciplinary project lead assigned to FDA review team to facilitate efficient review and serve as the scientific liaison
  - Organizational commitment involving FDA senior managers and experienced FDA review staff in a proactive collaborative, cross-disciplinary review

- By December
  - 121 requests received
  - 34 granted, about one third for genetic diseases
  - 3 approved already, 2 were for rare diseases

*11/22/13*
CDER Has Granted 34 Breakthrough Therapy Designations Since Inception

113 Requests
- Pending: 49%
- Granted: 30%
- Denied: 12%
- Withdrawn: 9%

34 Granted
- Antiviral: 24%
- Neurology: 18%
- Pulmonary / Allergy / Rheumatology: 9%
- Gastroenterology / Inborn Errors: 9%
- Cardiology / Renal: 6%
- Hematology: 3%
- Oncology: 3%
- Psychiatry: 3%

Data as of 11/30/2013
Breakthrough Therapies: Lessons Learned To Date

• All BT requests in CDER are reviewed by the Medical Policy Council to ensure consistency of standards and approach

• Some designated drugs have been late in development; in some cases the marketing application already submitted
  – Main focus of program is on identifying drugs early in development

• Clinical development often NOT the rate-limiting step
  – Manufacturing development and scale-up must be accelerated

• Program commitments are resource intensive for FDA
  – Number of requests and designations have exceeded expectations
Breakthrough Therapies: Lessons Learned (2)

• Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable; e.g., very small number of patients treated, anecdotal case reports
  - Failure to demonstrate “substantial” improvement over available therapy
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies that identify a subset that may benefit

  - Many represent “the triumph of hope over evidence”
Causes of Drug Shortages: Quality Manufacturing Issues

- Quality: Facility Remediation Efforts: 35%
- Quality: Product Manufacturing Issues: 14%
- Discontinuation of Product: 8%
- Raw Materials (API) Shortage: 6%
- Other Component Shortage: 4%
- Increased Demand: 2%
- Loss of Manufacturing Site: 1%
FDA’s Response to Potential Shortage: FDA Actions

- Strategic Plan released October 31, 2013
  - (Presidential directive 2011, FDASIA 2012)
  - Early Notification is the key and is required prompt attention
- Perform risk-based analysis to determine ways to address shortage
  - Determine if other manufacturers can increase production
  - Expedite inspections and reviews of submissions
  - Exercise temporary enforcement discretion for new sources of medically necessary drugs
  - Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
  - Review possible risk mitigation measures for remaining inventory
- Communicate effectively to stakeholders
- Long term: Improve manufacturing quality (OPQ)
Value of Early Notification:

The graph shows the number of shortages reported by injectables and all categories, with a focus on the value of early notification. The x-axis represents the calendar year, ranging from 2005 to 2012, and the y-axis represents the number of shortages. The graph includes bars for injectables - prevented, injectables - new, all - prevented, and all - new. The number of shortages is indicated for each year, with the bars showing the distribution of early notification's impact over time.
Proposed Office of Pharmaceutical Quality: Principles

- **Put patients first** by balancing risk and availability.
- Have one quality voice by integrating review and inspection across product lifecycle.
- Safeguard clinical performance by establishing scientifically-sound and clinically relevant quality standards.
- Maximize focus and efficiency by applying risk-based approaches.
- Encourage innovation by advancing new technology and manufacturing science.
- Put Quality over Compliance
- Attention on how well drugs are manufactured
- Metrics, i.e. lot failure
- Create an ability to examine Quality across the industry
Patient-Focused Drug Development under PDUFA V

• FDA’s drug benefit-risk assessment considers severity of disease condition and degree of unmet medical need—clinical context
  - Patients are uniquely positioned to inform FDA understanding of the clinical context

• Patient-Focused Drug Development is part of FDA commitments under PDUFA V
  - Convene at least 20 meetings on specific disease areas
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA analysis both during and outside of review
  - 2013 meetings included narcolepsy and muscular dystrophy
  - Feedback has been good
Disease areas to be the focus of meetings for FY 2014-2015

**FY 2014 – 2015**

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction
- Fibromyalgia
- Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease with persistent regurgitation symptoms on proton-pump inhibitors
- Neurological manifestations of inborn errors of metabolism
- Parkinson’s disease and Huntington’s disease
- Pulmonary arterial hypertension
- Sickle cell disease
Pediatric Rare Disease Voucher Program

- FDASIA
- FDA will award priority review voucher to sponsors of rare pediatric disease product application that meet certain criteria
  - Prevalence predominantly pediatric
  - New drug
  - Not seeking adult indication
- Can seek designation during development
- Voucher is transferable
- Formal guidance to be published
Regulatory Collaborations

- Enhanced international collaborations in recent years
- EU:
  - International Rare Disease research Consortium (IRDIRC)
    - Several FDA members participate
  - Harmonized orphan drug application form
  - Regular meetings on orphan drugs, cancer, and pediatrics
- NIH
  - CDER-NIH CC taskforce
  - IND regulatory training workshop
Rare Disease Priorities

- Significant percentage of novel product approvals
  - Trend expected to increase
- High use of expedited pathways and incentive programs
- Targeted therapies increasingly common in drug development
  - Common disease subsets → “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
  - Need for flexibility, novel trial designs, translational science development

Summary

- CDER initiatives in drug shortages, pharmaceutical quality, expedited reviews, pediatric rare disease vouchers, and patient informed decision making should have a significant impact on rare disease drug development.
- Rare Diseases have always been a leader in innovation and continue to do so.
Addendum
### Snapshot of CY 2013
#### NME NDAs/BLAs\(^\d\) Drug Approvals (1/2)

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<thead>
<tr>
<th>Trade Name</th>
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<th>Priority Approval</th>
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Data as of 11/30/2013

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\(\d\) Original BLAs that do not contain a new active ingredient are excluded

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date
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### NME NDAs/BLAs† Drug Approvals (2/2)

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