Regulatory Challenges with Cell and Gene Therapy

Adora Ndu, PharmD, JD, BioMarin Pharmaceutical Inc.
Disclaimer

• The views expressed in this presentation and included in the slides that follow are solely those of the presenter and do not reflect those of BioMarin Pharmaceuticals Inc.
Progression in Complexity of Available Therapy

- **Small molecules**
  - Chemically manufactured active substance
  - Targeted therapies

- **Biologics**
  - Large protein molecules
  - Protein engineering

- **Cell & Gene Therapy**
  - Transfer of genetic materials or cells into a patient
  - Potential to repair the direct cause of diseases through cell or gene programming
More Products Under Development

- **US**
  - 560 active INDs for gene therapies, with 82 submitted in 2016 alone*  
  - More than 1,100 different gene therapy trials but no approved gene therapy product

- **Europe**
  - Between 1999 and 2015, ~1000 clinical trials for advanced therapy medicinal products (ATMPs), 65 in Phase III+  
  - 5 ATMPs approved as of October 2015+

- **Japan**
  - 4 approved marketed products as of February 2016; 22 clinical trials initiated

---

**EMA Scientific recommendation on advanced therapy classification**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitted</td>
<td>22</td>
<td>19</td>
<td>12</td>
<td>22</td>
<td>20</td>
<td>28</td>
<td>61</td>
<td>60</td>
<td>14</td>
<td>258</td>
</tr>
</tbody>
</table>

*Senate HELP Committee hearing March 21, 2017
If an HCT/P does not meet the criteria in 21 CFR 1271.10(a), and the manufacturer doesn’t qualify for exceptions in 21 CFR 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under the FD&C Act, and/or section 351 of the PHS Act.
## Regulatory Classification: EU

- **Advanced Therapy Medicinal Products (ATMPs)** - medicines for human use that are based on genes or cells

| Gene Therapy | • Contain genes that lead to a therapeutic, prophylactic or diagnostic effect.  
|              | • Work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases |
| Somatic-cell therapy | • Contain cells/tissues that have been manipulated to change their biological characteristics  
| | • They can be used to cure, diagnose or prevent diseases; |
| Tissue-engineered medicines | • Contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue |
| Combined ATMPs | • Contain one or more medical devices as an integral part of the medicine. |
• (EC) No. 1394/2007 – Provides overall framework on ATMPs
• Part IV of Annex I to Directive 2001/83/EC provides definitions for gene therapy and somatic cell therapy
Regulatory Classification: Japan

• The Pharmaceutical Affairs Law was amended under Law No. 84/201 and renamed Pharmaceutical and Medical Device (PMD) Act.
• Amendment to include a chapter on regenerative medical products and introduce the new accelerated pathway.
• Regenerative Medical Products are defined as processed human cells that are intended to be used for:
  – The reconstruction, repair, or formation of structures or functions of the human body
  – The treatment or prevention of human diseases
  – Gene therapy
Targeted Regulatory Pathways

- **Japan** – Expedited approval system for regenerative medicine products
- **US** – Regenerative medicine advanced therapy (RMAT)
## Section 3033
**Accelerated Approval for Regenerative Medicines**
- Drug must be a regenerative medicine therapy; and "intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition"; and "preliminary clinical evidence indicates [it] has the potential to address unmet medical needs."

## Section 3034
**FDA Guidance on Regenerative Advanced Therapies**
- FDA guidance (draft by Dec. 2017), clarifying evaluation of devices used in the recovery, isolation, or delivery of RMAT.

## Section 3035
**FDA Report to Congress on Regenerative Advanced Therapies**
- FDA to report to Congress on RMAT applications and status.

## Section 3036
**Developing Standards for Regenerative Medicine**
- HHS/FDA standards and consensus definitions (Dec. 2018) to support development, evaluation, and review of RMAT.
- HHS/FDA update guidance and regulations regarding regenerative therapeutic products, and hold a public meeting to encourage innovation.
Regenerative Medicine - USA

• Section 3033 of 21st Century Cures defines regenerative medicine therapy as “cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations.”

• Was the intent to include HCT/Ps regulated under section 351 of the Public Health Service Act, including gene therapy, in this definition?
  – Gene therapy is included in similar definition and pathway in Japan
  – Section 3033 defining regenerative medicine therapy specifically excludes ONLY 361 HCT/Ps
<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Regenerative Medicine Advanced Therapy</th>
<th>Breakthrough Therapy Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>Eligible if:</td>
<td>Eligible if:</td>
</tr>
<tr>
<td></td>
<td>• Regenerative Medicine Therapy, and</td>
<td>• Intended to treat a serious condition; and</td>
</tr>
<tr>
<td></td>
<td>• Intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and</td>
<td>• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
</tr>
<tr>
<td></td>
<td>• Preliminary clinical evidence indicates [it] has the potential to address unmet medical needs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Regenerative Medicine Advanced Therapy</th>
<th>Breakthrough Therapy Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early dialogue with FDA regarding development</td>
<td>• Meetings with FDA throughout development of drug</td>
<td></td>
</tr>
<tr>
<td>• Possible eligibility for priority review</td>
<td>• Intensive guidance on efficient drug development</td>
<td></td>
</tr>
<tr>
<td>• Possible eligibility for accelerated approval (AA) based on 1) surrogate or intermediate endpoints or 2) reliance on data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate</td>
<td>• Organizational commitment (e.g. early involvement of senior managers)</td>
<td></td>
</tr>
<tr>
<td>• AA postapproval requirements (requirements will vary depending on FDA agreement)</td>
<td>• Rolling review</td>
<td></td>
</tr>
<tr>
<td>• e.g. use of patient registries, electronic health records, real world evidence or,</td>
<td>• Other actions to expedite review (e.g. Cross disciplinary project lead)</td>
<td></td>
</tr>
<tr>
<td>• Collection of larger confirmatory data sets or,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Postapproval monitoring of all patients treated with drug prior to approval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EU Consultation on Similarity

- European Commission launched a consultation (July 2016) regarding which products are to be considered “similar” as it applies to Orphan legislation.
- Proposal to update examples to include cell-based medicinal products and gene therapy medicinal products.
- Article 3 of Regulation 847/2000 on “similar medical products” requires adaptation to the field of advanced therapy medicinal products (ATMPs).
ATMPs may not be considered similar where:

- Principal molecular structural features cannot be fully defined and the similarity between two active substances needs to be assessed on the basis of biological and functional characteristics.

- Differences in starting materials or the final composition, or in manufacturing technology . . . have significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product.

- With two gene therapy products, there are differences in the therapeutic sequence, viral vector, transfer system or regulatory sequences that significantly affect the biological characteristics and/or activity relevant for the intended therapeutic effect of the product. . . Minor differences in the therapeutic sequence without a significant impact on the intended therapeutic effect are not sufficient to support the claim that two gene therapy medicinal products are non-similar.
## Consideration of Product Characteristics

<table>
<thead>
<tr>
<th>Product Characteristic</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector type (e.g. AAV)</td>
<td>• Tissue tropism, integration</td>
</tr>
<tr>
<td>Vector serotype</td>
<td>• Tissue tropism, biodistribution, immunogenicity, infectivity</td>
</tr>
<tr>
<td>Transduced sequence</td>
<td>• Amino acid sequence, glycosylation, tertiary structure</td>
</tr>
<tr>
<td>Non-coding regions of genome</td>
<td>• Control regions – promoter and enhancers affect expression level and tissue-specific transcription</td>
</tr>
<tr>
<td></td>
<td>• Regulators – regulates expression</td>
</tr>
<tr>
<td></td>
<td>• Introns – controls transcription/translation</td>
</tr>
<tr>
<td>Manufacturing system</td>
<td>• Differing host systems</td>
</tr>
<tr>
<td></td>
<td>• Vector to infective vector capsid ratio</td>
</tr>
</tbody>
</table>
Considerations for Similarity- ATMPs

- No precedent for determination of similarity assessments for ATMPs.
- Different criteria necessary for cell and gene therapy compared to small and large molecules.
- Setting specific criteria for ATMPs may be premature due to rapidly evolving landscape.
- Product characterization may require highly specific and proprietary methods.
- Clarity on what constitutes minor or major differences.
- Need examples of what is considered “significant impact on the intended therapeutic effect.”
- Clarity on when biological in vitro or in vivo data would be considered sufficient for demonstrating differences.
Regulatory Challenges

- Regulatory differences across different regions.
- Different product classifications and definitions across regions (e.g. regenerative medicine).
- Evolution of similarity for biologics based on structural analysis, manufacturing process and therapeutic target require modified framework specifically for cell and gene therapy.
Opportunities for Regulatory Collaboration

• Advanced-therapy medicinal product cluster
  – EMA, FDA, Health Canada

• International Pharmaceutical Regulators Forum (IPRF)
  – Meeting of international regulators, (including EMA, FDA, HC, TGA, KOR, PMDA).
  – IPRF Gene Therapy Working Group
    • To gain a common understanding of the regulatory framework within participating regions and an understanding of the classification of gene therapy products in participating regions
  – IPRF Cell Therapy Working Group
    • Convergence of regulatory approaches for cell and tissue-based therapies.

• Parallel scientific advice
Future Direction

• **Uniformity** in classification and **definition of regenerative medicine therapies to include gene therapy**.

• **Early** regulatory clarity and predictability on the sameness/similarity criteria for cell and gene therapy to continue to foster development.

• **Early** dialogue between health authorities and developers of cell and gene therapies is critical to supporting development.
Was the accelerated approval of EXONDYS 51 (eteplirsen) injection an outlier?

How will 21st Century Cures Authorities inform regulatory actions for drugs/biologics intended to treat rare serious and life-threatening conditions?
Disclaimer

• The views expressed are my own and not that of my employer.
• My views are informed only by a review of public records.
FDA grants accelerated approval to first drug for Duchenne muscular dystrophy

For Immediate Release
September 19, 2016

The accelerated approval of Exondys 51 is based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients. The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. A clinical benefit of Exondys 51, including improved motor function, has not been established. In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy.
Did the FDA set ‘a dangerous precedent' with its latest drug approval?

Damian Garde @damiangarde

September 19, 2016

The experimental drug that federal regulators approved Monday¹ will only be used by a few thousand patients.

But the approval may have set a precedent that could rocket through the health care system, opening the door for drug makers to get more medicines to market — even with scant evidence that they work.
Background on DMD and eteplirsen

- DMD X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene leading to near absence of dystrophin protein in muscle cells
- Absence of dystrophin leads to muscle damage, with replacement by fat and collagen, and concomitant loss of physical function; premature death from respiratory and/or cardiac failure in second to fourth decade
- Eteplirsen restores mRNA reading frame so that exon 51 is excluded leading to production of a truncated but partially functional form of dystrophin similar to that found in BMD
- Mutation amenable to exon 51 skipping affects 13% of DMD population (600 – 1300 patients)
Procedural History

- **Advisory Committee**, voted 6-7 against accelerated approval (April 25, 2016)
- **Center Director Decisional Memo**, Janet Woodcock (July 14, 2016)
  - Recommending Accelerated Approval
- **Office of Drug Evaluation-I Decisional Memo**, Ellis Unger (July 15, 2016)
  - Recommending a Complete Response Action
- **Agency Scientific Dispute Appeal**, Ellis Unger (July 18, 2016)
- **Scientific Dispute Resolution Appeal**, Luciana Borio (August 8, 2016)
  - Finding adequate opportunity to air and consider dissenting views and recommending substantive review of the scientific dispute
- **Commissioner’s Decision**, Robert Califf (September 16, 2016)
  - Defers to Dr. Woodcock’s judgment and authority

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf
**Issue:** Whether the quantity of dystrophin produced by eteplirsen is an effect reasonable likely to predict clinical benefit for accelerated approval purposes?

<table>
<thead>
<tr>
<th>Unger (Borio in agreement)</th>
<th>Agreement</th>
<th>Woodcock</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Only one interpretable study (301, n=13) supports expression of dystrophin</td>
<td>• Dystrophin production appropriate but not validated surrogate endpoint</td>
<td>• Two studies (201/202, n=13; 301, n=13) support expression of dystrophin</td>
</tr>
<tr>
<td>• Dystrophin in range of 10% of normal values (versus 0.22% to 0.32% seen in the study) needed to provide evidence of “reasonably likely” based on BMD model</td>
<td>• Dystrophin produced smaller than expected</td>
<td>• No rational basis to identify a specific threshold value for dystrophin levels to provide evidence of “reasonably likely”</td>
</tr>
<tr>
<td>• No evidence of functional improvement from studies</td>
<td>• Significant shortcomings in the development program</td>
<td>• Post-hoc analysis supportive of some functional improvement</td>
</tr>
</tbody>
</table>
Policy Arguments

**Unger**

- Where no evidence of efficacy has been provided, we should not accept the known and unknown safety risks
- Providing false hope to patients
- Withdrawing an accelerated approval drug where lack of confirmatory evidence is established is difficult
- Patients foregoing steroids
- Slowing research on drugs that may work
- Lowering of accelerated approval standard to unacceptable level
- Precedent setting
- FDA caving to political pressure and intimidation

**Woodcock**

- In this context, it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness
- Patients and physicians are generally willing to accept greater risks or side effects, including greater uncertainty about effectiveness, for products that treat life-threatening and severely debilitating illnesses where there are no therapeutic alternatives
- Takes note of the generally favorable safety profile
- Approval does not compromise the confirmatory trials that are underway
Was eteplirsen an outlier?

FDA’s Flexibility in Subpart H Approvals: Assessing Quantum of Effectiveness Evidence

FRANK J. SASINOWSKI*
ALEXANDER J. VAROND**

*Cataloging FDA’s Flexibility in Subpart H Approval*

<table>
<thead>
<tr>
<th>Table 1: Subpart H Scoring Rubric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Part 1:</strong> Rarity of the Disease</td>
</tr>
<tr>
<td><strong>Part 2:</strong> Understanding of the Disease Process</td>
</tr>
<tr>
<td><strong>Part 3:</strong> Understanding of Relationship Between the Drug’s Effect on the Unvalidated Surrogate and the Disease</td>
</tr>
<tr>
<td><strong>Part 4:</strong> Strength of Clinical Evidence</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Used with permission*
**Figure 1:** Cumulative Scores for Non-AIDS/Non-Cancer Subpart H Precedents (0–20)†

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rarity of the Disease</th>
<th>Rarity (0-2)</th>
<th>Understanding of the Disease (0-4)</th>
<th>Understanding of the Disease Process (Section VII.C.1)</th>
<th>Understanding of the Relationship Between the Drug’s Effect on Surrogate and the Disease (Section VII.C.2)</th>
<th>Surrogate Endpoint (0-7)</th>
<th>Clinical Benefit (0-3)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Northera</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2. Sirturo</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>-1</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Fennprof</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Makena</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Soliris</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Promacta</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Eziade</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Tyssiv</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Lueris</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Fabrazyme</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Remodulin</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Celebrex</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Synercid</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Remicade</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Pritin</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Sulfamylon</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Prokamine</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Baxin</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Betaseron</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean: 1.9±0.3  
Range: 1-2  
(out of 2)  

Mean: 2.8±1.2  
Range: 1-4  
(out of 4)  

Mean: 2.3±0.9  
Range: 1-4  
(out of 4)  

Mean: 5.3±2.2  
Range: 1-9  
(out of 10)  

---

1 These citations are to the FDA Guidance

2 Parts 2, 3, and 4 are also from FDC Act Sec. 506, as amended by FDASIA Sec. 901, specifically, FDASIA uses the following terms for each of these parts

- **Part 2** relates to “pathophysiological” evidence
- **Part 3** relates to “epidemiological, . . . Pharmacologic, or other evidence . . .”
- **Part 4** relates to “therapeutic” evidence

---

**Statistics**  
**Score**  
Average Score: 12  
Min: 8  
Max: 16  
Median: 12  
SD: 2.4

Used with permission
<table>
<thead>
<tr>
<th>Factor</th>
<th>Element within Factor</th>
<th>Rubric Results (n = 19)</th>
<th>eteplirsen (my assessment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarity of the Disease</td>
<td>Rarity of the disease</td>
<td>Mean: 1.9 ± 0.3&lt;br&gt;Range: 1 – 2&lt;br&gt;(out of 2)</td>
<td>2</td>
</tr>
<tr>
<td>Understanding the Disease Process</td>
<td>Understanding of pathophysiology of disease</td>
<td>Mean: 2.8 ± 1.2&lt;br&gt;Range: 1 – 4&lt;br&gt;(out of 4)</td>
<td>4</td>
</tr>
<tr>
<td>Understanding of Relationship between drug’s effect on the unvalidated surrogate endpoint and the disease</td>
<td>Understanding from epidemiological evidence, animal models, other similar pharmacologic class or other sources</td>
<td>Mean: 2.3 ± 0.9&lt;br&gt;Range: 1 – 4&lt;br&gt;(out of 4)</td>
<td>2</td>
</tr>
<tr>
<td>Strength of clinical evidence</td>
<td>Clinical evidence on surrogate or ICE</td>
<td>Mean: 5.3 ± 2.2&lt;br&gt;Range: 1 – 9&lt;br&gt;(out of 10)</td>
<td>2 (out of 7)</td>
</tr>
<tr>
<td></td>
<td>Clinical evidence benefit</td>
<td>0 (out of 3)</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td><strong>Average Score</strong></td>
<td><strong>12</strong></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td><strong>Min</strong></td>
<td><strong>8</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Max</strong></td>
<td><strong>16</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Median</strong></td>
<td><strong>12</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Standard Deviation</strong></td>
<td><strong>2.4</strong></td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission
Application of select 21st Century Cures Authorities to our Case Study

- Patient-Focused Drug Development
- Qualification of drug development tools
- Targeted drugs for rare diseases
- Real World Evidence
An additional factor in this situation is the emergence of patient-centered drug development and the extensive interactions with the patient community as part of the overall environment for development and decision-making. While the appropriate methods for patient-centered drug development are evolving, the fact that DMD involves vulnerable children with a life-threatening illness and understandably concerned parents produces significant pressure on all involved. This dynamic is well reflected in Dr. Unger and Dr. Woodcock’s documents. With a significant history dating back to the development of drugs for HIV/AIDS, patient-focused drug development is not an entirely new component of FDA’s regulatory process, and it remains an explicit CDER priority in the current era.
Patient-Focused Drug Development

Patient Experience Data – Jett Foundation
Provided to FDA and Presented at AdCom

Study 204: Daily Diary of Patient C
Spontaneous Collapses

- Collapses Per Day (Mean)

- Started Drug

- November 2014*
- December 2015
- January
- February
- March
- April
- May

*Began in Study 204 eteplirsen safety trial in mid-November 2014

“Other” Input

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

“Dear Dr. calif: How is it that everyone in and around DMD understands this simple idea and the science geniuses at FDA don’t? You stupid f__kers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

f__king clue

(b)(6)

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

Ellis Unger, Agency Scientific Dispute Appeal
Patient Focused Drug Development, §§ 3001-3004

- Encourages drug sponsors and FDA to incorporate “patient experience data” into the drug development and review process
- “Patient experience data” is defined as data that are intended to provide information about patients’ experiences with a disease or condition, including (i) the impact of such disease or condition, or a related therapy, on patients’ lives, and (ii) patient preferences with respect to treatment of such disease or condition
- Within six months of enactment, plan to issue draft and final version of guidance documents over a period of five years regarding the collection of patient experience data and the use of such data in drug development
Qualification of Drug Development Tools, § 3001

• Codifies a process for qualifying drug development tools, which may be used to support a new drug application (NDA), a biologics license application (BLA), or an investigational new drug application (IND)
• Drug development tools can include biomarkers (including surrogate endpoints), clinical outcome assessments, or other methods, materials, or measures determined to aid drug development and regulatory review
• This provision will bolster FDA’s existing drug development tool qualification program
Targeted Drugs for Rare Diseases, § 3012

- Allows for more streamlined development of genetically-targeted drugs and variant protein-targeted drugs that address unmet medical need in rare disease subgroups
- Under this provision, sponsors of targeted drugs may rely on data from studies previously conducted by the same sponsor (or another sponsor with a contractual right of reference) and submitted in previously approved applications for drugs using the same or similar targeted technology
- Value appears to be the explicit recognition of relevance of prior data that incorporates or utilizes the same or similar genetically targeted technology or the same variant protein targeted drug
Real World Evidence, § 3022

- Requires FDA to establish a program and issue guidance to increase the collection, use, and reliance of real-world evidence to help support regulatory decision-making
- This section would encourage the use of real-world evidence to help support (i) approval of a new indication for a drug already approved pursuant to an NDA, and (ii) post-approval study requirements
- Defines “real-world evidence” to mean data regarding the use, benefits, or risks of a drug “derived from sources other than randomized clinical trials,” which would include, for example, ongoing safety surveillance, observational studies, and registries