FDA Evaluation and Approval of Drugs for Rare Diseases

Child Neurology Society
Symposium on Rare Diseases
October 9, 2015

Frank Sasinowski, M.S., M.P.H., J.D
Hyman, Phelps & McNamara, P.C.
Adjunct Professor of Neurology, University of Rochester
FJS@hpm.com

Financial Disclosure: “I represent many pharmaceutical companies with therapies in development for many neurological disorders.”
Overview

I. FDA Orphan Drug Flexibility
II. FDA Subpart H Approvals
III. Emerging Role of the Patient Voice
Section I –
FDA Orphan Drug Flexibility
Purpose:

– Examine whether FDA exercises flexibility when reviewing applications for orphan diseases

  • If so, illustrate the nature and scope of that flexibility

†Sasinowski, F., “Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloging FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders”, Drug Information Journal, vol. 46(2), 238-263 (2012).
I. Original Methods

• Original 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
  – 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 his 2012 analysis (22%) and on 5 of 27 drugs in this new update (19%)
I. Quantum of Evidence Required

• Efficacy evidence required under the federal Food, Drug, and Cosmetic 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

• 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)
I. 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
I. DIA’s March 2012 Drug Information Journal and Impact

Immediate Uptake:


Continuing Impact:

- FDA Dr. Andrew Mulberg’s introductory statement to Nov. 2013 Advisory Committee on Vimzim for Morquio (MPS IVA)
- J. Woodcock’s 21 Century Cures Initiative testimony, July 2014
- FDA “Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases . . .,” July 2014
## I. Results of 2012 Sasinowski Analysis

<table>
<thead>
<tr>
<th>Chemical and Brand Names</th>
<th>Approval Date</th>
<th>Type of Efficacy Evidence</th>
<th>“Total Flexibility” Combination of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conventional</td>
<td>Administrative Flexibility</td>
</tr>
<tr>
<td>Agalsidase betal</td>
<td>04/2003</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Albendazole – Albenza</td>
<td>06/1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alglucerase – Ceredase</td>
<td>04/1991</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine – Retrovir</td>
<td>03/1987</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Zoledronic Acid – Zometa</td>
<td>08/2001</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotals:</strong></td>
<td><strong>45</strong></td>
<td><strong>32</strong></td>
<td><strong>58</strong></td>
</tr>
<tr>
<td><strong>Flexibility?</strong></td>
<td>Not Needed: 45</td>
<td>Yes: 90</td>
<td></td>
</tr>
</tbody>
</table>
I. Results of 2012 Sasinowski Analysis

• From 1983 – 2010: 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
I. Updated Analysis

- Updated analysis\textsuperscript{†} classifies the approval of the 27 orphan drugs approved between July 1, 2010 - June 30, 2014 (excluding cancer therapies, as was done in 2012 analysis)

- Follow up to the 2012 Sasinowski analysis and paper

- To determine whether, over the past four years, FDA has required orphan drug applications to meet the same statutory standards of effectiveness that is ordinarily expected for most drugs for prevalent diseases

- 2012 analysis was conducted solely by Sasinowski; this update was conducted jointly by Erika Panico of Chiesi, James Valentine of HPM, and Sasinowski

I. Results for Update

<table>
<thead>
<tr>
<th>Chemical and Brand Names</th>
<th>Approval Date</th>
<th>Type of Efficacy Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conventional</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Bedaquiline – Sirturo</td>
<td>12/2012</td>
<td></td>
</tr>
<tr>
<td>2 Belatacept – Nulojix</td>
<td>06/2011</td>
<td>✓</td>
</tr>
<tr>
<td>3 Botulism antitoxin</td>
<td>03/2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 Tasimelteon – Hetlioz</td>
<td>01/2014</td>
<td>✓</td>
</tr>
<tr>
<td>27 Teduglutide (rDNA origin)</td>
<td>12/2012</td>
<td></td>
</tr>
</tbody>
</table>

Subtotals: 8
Flexibility? Not Needed: 8
Yes: 19
## I. Update to Orphan Drug Analysis

<table>
<thead>
<tr>
<th>Orphan Drug Efficacy Evidence</th>
<th>Conventional</th>
<th>Total Flexibility</th>
<th>“Total Flexibility” Combination of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Administrative</td>
</tr>
<tr>
<td><strong>2012 Sasinowski Analysis</strong></td>
<td>45 (33.3%)</td>
<td>90 (66.7%)</td>
<td>32</td>
</tr>
<tr>
<td><em>(1/83 – 6/10)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2014 Update</strong></td>
<td>8 (29.6%)</td>
<td>19 (70.4%)</td>
<td>14</td>
</tr>
<tr>
<td><em>(7/10 – 6/14)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>53 (32.7%)</td>
<td>109 (67.3%)</td>
<td>46</td>
</tr>
</tbody>
</table>
### I. Analysis of Orphan Drug Efficacy by Decade (Updated)

<table>
<thead>
<tr>
<th>Orphan Drug Efficacy Evidence</th>
<th>Conventional</th>
<th>Total Flexibility</th>
<th>“Total Flexibility” Combination of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period</td>
<td></td>
<td></td>
<td>Administrative</td>
</tr>
<tr>
<td>1983* - 1989</td>
<td>7 (33.3%)</td>
<td>14 (66.7%)</td>
<td>5</td>
</tr>
<tr>
<td>1990 – 1999</td>
<td>21 (35.6%)</td>
<td>38 (64.4%)</td>
<td>13</td>
</tr>
<tr>
<td>2000 – 2009</td>
<td>13 (26.5%)</td>
<td>36 (73.5%)</td>
<td>13</td>
</tr>
<tr>
<td>2010 – 2014**</td>
<td>12 (37.5%)</td>
<td>21 (63.6%)</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>53 (32.7%)</td>
<td>109 (67.3%)</td>
<td>46</td>
</tr>
</tbody>
</table>

* Beginning in January 1983, the date of enactment of the Orphan Drug Act.
** Through June 30, 2014.
I. Conclusions on Orphan Drug Act Analysis

• Original 2012 analysis showed that:
  – FDA historically exercised regulatory flexibility in approving therapies for Americans with rare diseases

• This 2015 update shows that:
  – FDA continues to regularly exercise this regulatory flexibility

• This update, together with the original 2012 analysis, should further aid FDA’s regulation of therapies for persons with rare diseases
Section II –
FDA Subpart H Approvals
II. Subpart H – Four Recent Milestone Events: #1

FDA Safety and Innovation Act (FDASIA) – July 2012
II. Subpart H – Four Recent Milestone Events: #1

• In July 2012, FDASIA refined the starting “Fast Track” codification of 21 C.F.R. Part 314, Subpart H, by defining a Subpart H therapy in this way:
  – “a product for a serious or life-threatening disease . . . that . . . has an effect on a surrogate . . . that is reasonably likely to predict clinical benefit, or on a clinical endpoint . . . , taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”
II. Subpart H – Four Recent Milestone Events: #2

President’s Council of Advisors on Science and Technology Report (PCAST) – Sept. 2012

- “FDA’s interpretation of ‘reasonably likely . . . to predict’ can have a major impact on the pace of medical innovation . . . .”
- “Historically, the use of [Subpart H] has been primarily used in a limited number of therapeutic areas—principally, HIV/AIDS, cancer, and inhalation anthrax (87 percent of cases) . . . .”
- “We believe that the Nation would benefit if the FDA were to expand the use in practice of acceptable indicators to other serious or life-threatening diseases.”
- “The FDA should expand the use in practice of its existing authority for Accelerated Approval.”
- “FDA should direct its staff, across all divisions, to make full use of the Accelerated Approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious . . . illness and demonstrating an effect on a clinical endpoint (other than survival or irreversible morbidity) or on a surrogate endpoint that is reasonably likely to predict clinical benefit.”
II. Subpart H – Four Recent Milestone Events: #3

FDA’s Guidance, “Expedited Programs for Serious Conditions–Drugs and Biologics” – May 2014

- Lists and describes Factors that FDA views as critical to Accelerated Approval/ Subpart H
II. Subpart H – Four Recent Milestone Events: #4

Energy & Commerce Committee’s Subcommittee on Health

- Congress comprehensively addressing medical product development
  - Frank’s testimony focused on increasing visibility to Subpart H
II. Purpose of Sasinowski/Varond Subpart H Analysis

• To promote a better understanding of the circumstances under which Subpart H may be employed in order to:
  – Facilitate the development and expedited review of new drugs with the potential to address unmet medical needs for serious and life-threatening illnesses
  – Mobilize expanded FDA use of Subpart H

• To examine and describe the evidentiary foundation for FDA’s determinations that an unvalidated surrogate or clinical endpoint was “reasonably likely to predict” patient benefit sufficient to meet statutory standard of substantial evidence of effectiveness

II. Methods

• Identified FDA’s 19 Subpart H approvals for conditions other than HIV/AIDS or cancer*

• Provided analysis with narrative text describing most relevant information pertinent to each Factor listed in FDA Guidance
  – Including clinical evidence on the surrogate and, where available, on ultimate clinical benefit
    • FDA said it could not address this most critical of factors in its guidance because the clinical evidence is not “generalizable.”
    • In this analysis, we then chose not to generalize, but to describe specifics of each precedent.

* Also approved under Subpart H, via the “Animal Rule,” but not included in this analysis, are Levaquin and Cipro.
II. Methods

Scoring (20-point scale)

• **Part 1**: Rarity of Condition (2 points)

• **Part 2**: Understanding of the Disease Process (4 points)
  – Understanding of the pathophysiology of the disease

• **Part 3**: Understanding of Relationship Between the Drug’s Effect on Surrogate and the Disease (4 points)
  – This understanding may come from epidemiological evidence, animal models, other drugs in similar pharmacologic class or other sources

• **Part 4**: Strength of Clinical Evidence (10 points)
  – Clinical evidence for surrogate (7 points)
  – Clinical evidence of benefit (3 points)
II. Results Scored by Factors in FDA’s Guidance (by Decade)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Number of Subpart H Approvals</th>
<th>Average Score (Max. Score of 20 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990 – 1999</td>
<td>8</td>
<td>11.75</td>
</tr>
<tr>
<td>2000 – 2009</td>
<td>6</td>
<td>13.33</td>
</tr>
<tr>
<td>2010 – 2015*</td>
<td>5</td>
<td>12.0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>12.32</td>
</tr>
</tbody>
</table>

* Through May 4, 2015, and normalized to a full dated: 9.5 approvals.
II. Results – Summary

Score Card

- **Part 1**: Rarity of Condition
  - Range: 1 - 2 points (out of maximum of 2)
  - Findings:
    - Scores were consistently high

- **Part 2**: Understanding of the Disease Process
  - Range: 1 - 4 points (out of maximum of 4)
  - Findings:
    - Although a clear understanding of the pathophysiology of the disease process will facilitate reliance upon a surrogate, the absence of a complete understanding of the disease process is not incompatible with Subpart H (e.g., Remicade)
    - “Crohn's disease most likely represents a heterogeneous group of disorders. After much effort that has focused on the identification of a specific pathogenic cause, it is being recognized that disease manifestations could result from a combination of any, or all of, a number of factors.” (Medical Review at p. 2).
II. Results – Summary

Score Card

• **Part 3:** Understanding of the Relationship Between the Drug’s Effect on Surrogate and the Disease
  – Range: 1 - 4 points (out of maximum of 4)
  – Findings:
    • Although a strong understanding of the relationship between the drug’s effect on surrogate and the disease is helpful, a weaker showing is not a bar to Subpart H (e.g., Fabrazyme)

• **Part 4:** Strength of Clinical Evidence
  – Range: 1 - 9 points (out of maximum of 10)
  – Findings:
    • **Clinical evidence on the surrogate:** This is the most important approval factor to FDA reviewers and received the most weight; however, a low score here was still not a bar to approval, see e.g., Sulfamylon and Synercid
    • **Clinical evidence of benefit:** 10 of 19 precedents had essentially no substantial positive evidence of clinical benefit (and one, Sirturo, was even negative)
Betaseron (multiple sclerosis) (FDA's first Subpart H approval)

- **Part 1**: Regulatory Factors Weighing into FDA Determination
  - **Rarity of Condition – 2 of 2 pts**
    - Designated as orphan drug on November 17, 1988

- **Part 2**: Understanding of the Disease Process
  - **Understanding of the disease – 2 of 4 pts**
    - Pathophysiology of MS was known to a fair degree at the time of the conduct of the pivotal trial which permitted sponsor and FDA to have general agreement on co-primary endpoint of clinical utility related to exacerbations, but the understanding of the role of the somatic measure of the putatively key causal biologic marker, MRI lesion volume, was not definitively established.
Betaseron (multiple sclerosis) (cont’d)

• **Part 3**: Understanding of Relationship Between MRI Lesion Volume and Multiple Sclerosis – 3 of 4 pts
  – At the FDA Advisory Committee, there was a strong feeling among “many experts” that “the number and area of lesions detected on MRI are tantamount to a ‘surrogate’ endpoint that predicts disease progression in MS.” The strength of this *opinion* actually “surprised” the key FDA reviewers.

• **Part 4**: Clinical Evidence on MRI Lesion Volume and on Reduction in Exacerbations of MS
  – **Clinical evidence for MRI Lesion Volume – 7 of 7 pts**
    • P-value for comparison between Betaseron and placebo arms ranged from 0.03 to 0.001, depending upon the analysis used.
  – **Evidence of reduction in exacerbations – 2 of 3 pts**
    • Primary efficacy evaluations were based on reduction of exacerbations per subject and proportion of exacerbation-free subjects.
      – Met the first co-primary endpoint, reduction of exacerbations per subject, with a p-value of 0.0001.
      – Failed on the second co-primary endpoint, proportion of exacerbation-free subjects, with a p-value of 0.094.
II. Conclusions

• This analysis of Subpart H precedents demonstrates FDA’s flexibility:
  – Robust compliance with Factors 2, 3, and 4 cited in FDA’s May 2014 Guidance is not required

• This analysis also:
  – Clarifies the basis for existing FDA’s Subpart H approvals
  – May open this pathway to more therapies for patients with serious illnesses in need of therapy

May 13, 2015
Section III –
Emerging Role of the Patient Voice
A key part of regulatory decision making is establishing the context in which the particular decision is made. For purposes of drug marketing approval, this includes an understanding of the severity of the treated condition and the adequacy of the available therapies. Patients who live with a disease have a direct stake in the outcome of FDA’s decisions and are in a unique position to contribute to the Agency.

– Food and Drug Administration (in Federal Register notice announcing the Patient-Focused Drug Development program)
III. Overview of Formal FDA Interactions with Patients

- **Traditional Patient Interactions**
  - FDA Patient Representative Program (Advisory Committee role)

- **New Initiatives under FDASIA**
  - FDASIA Section 1137 “Patient Provision”
  - PDUFA V Structured Benefit-Risk Assessment Framework
  - PDUFA V Patient-Focused Drug Development
• Founded in late 1980’s in response to HIV/AIDS crisis, expanded in 1990’s under Clinton’s Cancer Initiative

• Role of the FDA Patient Representative:
  – Provide FDA with the unique perspective of patients and family members directly affected by serious or life-threatening disease.
  – Potential to serve in several ways, including:
    • On Advisory Committees (Often)
    • As Consultants to Review Divisions (Almost never)
Traditional Role of Patient Representative in Medical Product Development and Review

- Basic Research/Discovery
- Translational
- Translational Gap
- Pre-IND
- IND
- Clinical
- Ph 1
- Ph 2
- Ph 3
- ~5-10 years
- Ph 4
- ~5-10 years
- undefined
- ongoing
- NDA/BLA Review
- Post-marketing
- NDA/BLA
- Patient Voice Only Here
- Advisory Committee

Drug Developers

FDA
Food and Drug Administration
Safety and Innovation Act
Section 1137 “Patient Provision”
• FDA must “develop and implement strategies to solicit the views of patients during the medical product development process and consider their perspectives during regulatory discussions.”

• This could include FDA including a Patient Representative as a Special Government Employee (SGE) to be a part of the internal FDA review team and participate in meetings with medical product sponsors.
Post-FDASIA Role of Patient Representative in Medical Product Development and Review

Drug Developers

Basic Research/Discovery

Translational Gap

Translational

Pre-IND

IND

Clinical

Ph 1

Ph 2

Ph 3

Ph 4

NDA/BLA

NDA/BLA Review

Post-marketing

FDA

Advisory Committee

Patient Roles Throughout the Process

undefined

~5-10 years

~5-10 years

~5-10 years

~5-10 years
• Ms. House is President of the Acid Maltase Deficiency Association.

• Speaking at FDA’s Rare Disease Patient Advocacy Day, March 1, 2012.

• After the Myozyme review, FDA medical reviewers told me that they learned from Ms. House that being stable for a person with a uniformly progressive disease is a **HUGE** benefit.

• Patient perspective is a key factor for evaluating both safety and efficacy.
PDUFA V Patient-Focused Drug Development & Structured Benefit-Risk Assessment Framework
• Assessment of a drug’s benefits and risks involves analysis of severity of condition and current state of the treatment armamentarium

• Patients who live with a disease have a direct stake in drug review process and are in a unique position to contribute to drug development

• However, current approach to patient input generally relies on feedback received at FDA Advisory Committee meetings

• Review process could benefit from broader and more systematic approach to obtaining patient perspective on disease severity and unmet medical need by therapeutic or disease areas
• PDUFA V includes dedicated resources to expand activities that will provide review divisions with patient input

• FDA will convene meetings with stakeholders focused on specific disease areas during PDUFA V
  – Four public workshops per year—a minimum of 20 meetings over 5 years
  – Each meeting features a different disease area, reviewing the armamentarium for that indication, and identifying areas of unmet need
  – Participants include FDA review staff, the relevant patient advocacy community, and other interested parties
III. Disease Area Meetings

Meetings Planned for FY 2016 – 2017
- Non-tuberculous mycobacterial infections: October 15, 2015
- Alopecia areata
- Autism
- Hereditary angioedema
- Patients who have received an organ transplant
- Psoriasis
- Neuropathic pain associated with peripheral neuropathy
- Sarcopenia

Meetings Held in FY 2014
- Sickle Cell Disease: February 7, 2014
- Fibromyalgia: March 26, 2014
- Pulmonary Arterial Hypertension: May 13, 2014
- Neurological Manifestations of Inborn Errors of Metabolism: June 10, 2014
- Hemophilia A, Hemophilia B, von Willebrand disease, and Other Heritable Bleeding Disorders: September 22, 2014
- Idiopathic Pulmonary Fibrosis: September 26, 2014

Meetings Planned for/FY 2015
- Female Sexual Dysfunction: October 27-28, 2014
- Breast Cancer: April 2, 2015
- Chagas Disease: April 28, 2015
- Functional GI Disorders: May 11, 2015
- Parkinson’s Disease and Huntington’s Disease: September 22, 2015
- Alpha-1 Antitrypsin Deficiency: September 29, 2015

Meetings Held in FY 2013
- Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: April 25-26, 2013
- Lung Cancer: June 28, 2013
- Human Immunodeficiency Virus (HIV): June 14, 2013
- Narcolepsy: September 24, 2013
### III. CDER Benefit-Risk Assessment Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Unmet Medical Need</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Benefit</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Risk</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Summary of evidence:</td>
<td>Conclusions (implications for decision):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit-Risk Summary and Assessment</td>
</tr>
</tbody>
</table>
III. Informing Benefit-Risk

• **Analysis of Condition:**
  – What is the treated (or prevented) condition?
  – What are its clinical manifestations (i.e., symptoms that are either reported or observed)?
  – What is known about the natural history and progression of the condition, including in specific subpopulations?
  – How severe is the condition for those who have it?
    – How does severity vary across the sub-populations we have defined? (Note specific subpopulations and nature of differences.)
  – What is the basis for our assessment of the condition and its severity? (Note any relevant literature, clinical experience, expert opinion, etc.)
  – What are the major uncertainties in the available information? What are their implications?

• **Unmet Medical Need:**
  – What other pharmacological therapies are approved for this condition?
  – How effective and well-tolerated are these alternative therapies?
    – How do their effectiveness and tolerance vary by sub-population?
  – What off-label pharmacological therapies or non-pharmacological might be considered?
    – How effective and how well tolerated are they reported/believed to be?
  – What kinds of evidence are available about the use of alternative treatments for this condition?
  – What is the strength of evidence in each case?
  – What are the major uncertainties in the evidence? What are the implications of any uncertainty?
### III. Incorporating Patient Input into a Benefit-Risk Assessment Framework

#### The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration’s (FDA’s) Patient-Focused Drug Development Initiative

**Narcolepsy**

**Public Meeting: September 24, 2013**  
**Report Date: June 2014**

Center for Drug Evaluation and Research (CDER)  
U.S. Food and Drug Administration (FDA)

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy is a chronic neurological condition. The disease can have a debilitating effect on patients' day-to-day functioning and take a significant physical, emotional, and social toll on patients' quality of life.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analysis of Condition**

- Narcolepsy is a chronic disorder of the central nervous system characterized by dysregulation of sleep-wake cycles.
- An estimated 1 in 2,000 Americans are affected by narcolepsy although many who are affected remain undiagnosed.
- Symptoms vary from patient to patient and generally first appear between ages of 7 and 25 years. Symptoms include excessive daytime sleepiness, cataplexy, disturbed nighttime sleep, automatic behaviors, cognitive impairments, and difficulty concentrating.
- Symptoms can have a substantial effect on ability to function at school, work or in the home and to engage in social situations. Patients report that these effects result in stigmatization and have negative impacts on their education, jobs, families, and relationships.
- Refer to the Voice of the Patient report for a more detailed narrative.

**Current Treatment Options**

- There are five FDA-approved drug treatments for narcolepsy including:
  - Provigil (modafinil) and Nuvigil (armodafinil) are stimulants indicated to improve wakefulness in adult patients with excessive daytime sleepiness. Side effects include headache, dizziness, insomnia, increased heart rate and, rarely, serious rash.
  - Xyrem (sodium oxybate) is a depressant indicated for the treatment of cataplexy and excessive daytime sleepiness. The drug is taken at bedtime followed by another dose 2.5–4 hours later. Side effects include drowsiness, respiratory depression, automatic behaviors, and hallucinations. The drug is available through a restricted access program, and is a Schedule III controlled substance.
  - Other prescription stimulants, depressants, and antidepressants are also used off-label.
  - Most patients include scheduled naps, diet modification, and other lifestyle changes as part of their symptom management.
- Drug treatments are available for the symptoms of narcolepsy; however, efficacy varies from patient to patient, and significant side effects can limit benefits or preclude use of these medications. Thus, there is a continued need for additional effective and tolerable treatment options for patients to improve their daily functioning.
- Refer to the Voice of the Patient report for a more detailed narrative.
III. Informal Patient Interactions

When a Patient Speaks
By James E. Valentine*

Whether you call it “patient advocacy,” “patient engagement,” or maybe something a little fancier, in recent years incorporating the patient perspective has become a hot topic for FDA and drug developers alike. As FDA stated in announcing its Patient Focused Drug Development Initiative, this is because “patients who live with a disease have a direct stake in the outcome of FDA’s decisions and are in a unique position to contribute to the understanding of their disease” (78 Fed. Reg. 21,613 (April 11, 2013)).

There has been much collaboration between FDA, industry, and patient groups to identify best practices for engaging patients and to conduct pilot programs that solicit patient input. In the midst of all of these larger efforts, I wanted to share a recent experience that very simply demonstrates the value and impact of the patient voice.

Earlier this year CDER was being asked for input by a sponsor seeking to enter phase 3 of development for a rare disease. It is not uncommon in rare diseases for the FDA review staff to not have direct clinical experience with the disease or a nuanced scientific understanding of the disease. To the sponsor and the expert consultants for the rare disease, the novel CDER approach to understanding the

*What Legal Authority Does FDA Have to Regulate Medical Device Promotion on Internet Social Media Platforms? | Main | Legislation Would End "Constructive Transfer" and Change CSA Definition of "Dispense" to Permit Pharmacy Delivery of Controlled Substances to Physicians for In-Office Administration »

Search

Recent Posts
- In Appeal Over Colluding 505(b)(2) Approval, Plaintiffs-Appellants and PhRMA Meets Lower Court Decision Upsets Hatch-Waxman Scheme
- Multiple Parties Chime in as the Federal Circuit Gears Up for a Rerun in the ZARDOZ Biologics Case
- Patent Dance: 160-Day Notice Appeal
- Waking From a Drug Coma: How to Bring a Drug Out of Discontinued Status — It’s As Easy As 1, 2, 3...
- Velvet Ropes Can’t Stop the FDA: Effort to Defeat FDA Jurisdiction Based on Club Membership in Unmercifully Bounced

180-Day Exclusivity Tracker
- 180-Day Exclusivity Tracker [5+Mb]
III. Other Emerging Opportunities for Patient Input

Guidance for Industry
Duchenne Muscular Dystrophy
Developing Drugs for Treatment over the Spectrum of Disease

June 25, 2014

Guidance Document Submission
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dr. Janet Woodcock
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Dr. Janet Woodcock and colleagues at the FDA,

This correspondence constitutes a formal submission of a draft guidance authored by a consortium of stakeholders, under the coordination of Parent Project Muscular Dystrophy (PPMD), for consideration by the Food and Drug Administration (FDA). This material is intended as a submission to the docket as provided under the advice from the FDA’s good guidance practice work group, with the expectation that FDA will seriously consider adoption of all or significant sections of this submission.

When FDA, PPDMD and other interested parties met on December 12, 2013 in the spirit of public-private partnership to convene a Duchenne policy forum, we discussed the challenges designing and implementing clinical trials for rare diseases like Duchenne muscular dystrophy and the need to develop guidance to help accelerate development and the review of potential therapies for Duchenne muscular dystrophy (Duchenne). The forum concluded with an agreement that the Duchenne community, led by PPMD, would develop the first draft guidance on Duchenne for industry.

After an intensive five month process, overseen by a steering committee, developed by working groups composed of clinical experts, developers and patients, and further reviewed by a community advisory board, we are pleased to hereby present to you the Duchenne muscular dystrophy community’s draft of the Guidance for Industry: Duchenne Muscular Dystrophy: Developing Drugs for Treatment over the Spectrum of Disease, the first-ever patient advocacy-initiated draft guidance for a rare disease, written to help accelerate the development and review of potential therapies for Duchenne muscular dystrophy (Duchenne).

Our submission is prefaced by the Duchenne Imperatives, which begins with a few case studies, summarizes the document’s key points, and explicates the Duchenne community’s key imperatives — what we hope will be the take home messages from the community for the sponsor, the academic community and for the FDA, and to serve to frame the importance of the development of guidance for the community. We understand that the FDA may choose not to formally adopt this package, though it is hoped that such information will inform FDA’s deliberations regarding adoption of the formal draft guidance, which follows.
Thank you
FJS@hpm.com