Orphan Drug Topics:

1. Discovery of FDA’s Flexibility
2. Evolving Voice of the Patient in Drug Review

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Overview

I. Orphan Drug Flexibility
II. Role of Patient Advocates in Drug Approval Process

Conflict Statement: Mr. Sasinowski is an attorney and represents numerous pharmaceutical companies and patient groups in the drug arena. DC Bar Ethics Rules prohibit disclosure of specific clients.
Part 1 –
Orphan Drug Flexibility
Linked to Malformed Babies

‘Heroine’ of FDA Keeps Bad Drug Off of Market

By Morton Mintz
Staff Reporter

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophecies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable — even, she said, stupid. That such attributes could have been ascribed to her is, by her own acknowledgment, not surprising, considering all of the circumstances.

What she did was refuse to be hurried into approving an application for marketing a new drug. She regarded its safety as unproved, despite considerable data arguing that it was ultra safe.

It was not until last April, 19 months after the application was filed with the FDA, that the terrible effects of the drug abroad were widely reported in this country. What remains to be told is how and why Dr. Kelsey blocked the introduction of the drug before those effects were suspected by anyone.

Dr. Kelsey invoked her high standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1310 offspring, none was delivered with "evidence of malformation."

In a separate study, one rat did deliver a malformed offspring, but the dosage had been 1200 times the usual one. Rabbits that were injected with six times the comparable human dose also were reported to have produced no malformed births.

Recently, the FDA publicly

See DRUG, A5, Col. 1
FDA’s “Gold Standard” for Approval

- 1962 Amendments to the Federal Food, Drug, and Cosmetic Act
  - Drug approval requires “substantial evidence...consisting of adequate and well-controlled investigations, including clinical investigations” such that the Agency can conclude that the drug will have the effects that it is purported or claimed to have in its proposed labeling. FD&C Act § 505(d).

- FDA’s general interpretation: a minimum of two adequate and well-controlled clinical studies

- This means that each controlled trial must meet its primary endpoint by its pre-specified primary analysis and is statistically significant (a $P$ value of $\leq .05$)
Another public health problem

- Drug companies were not developing drugs to treat rare diseases
- As a result, in 1983, Congress passed the Orphan Drug Act
  - Has led to the approval of over 500 orphan drugs
- However, the law does not amend the FD&C Act’s “substantial evidence” of effectiveness standard
  - A vast majority of the estimated 7,000 rare diseases that, combined, affect about 30 million Americans are still without approved therapies
Purpose:

– Examine whether FDA exercises flexibility when reviewing applications for orphan diseases
  • If so, illustrate the nature and scope of that flexibility

Original Scope:

– 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 (primarily medical and statistical reviews)
  • Classified the level of “efficacy evidence” determined by FDA to be adequate for drug approval
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

3. “Case-by-Case Flexibility”
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.
The 2015 Updated Analysis

- Updated analysis classifies the approval of the 27 non-cancer orphan drugs approved between July 1, 2010 - June 30, 2014

- 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
The 2015 Updated Analysis

Published online first in Therapeutic Innovation and Regulatory Science (April 27, 2015)

doi:10.1177/2168479015580383

<table>
<thead>
<tr>
<th>Orphan Drug Efficacy Evidence</th>
<th>Conventional</th>
<th>Total Flexibility</th>
<th>“Total Flexibility” Combination of:</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Administrative</td>
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<tr>
<td>2012 Sasinowski Analysis</td>
<td>45 (33.3%)</td>
<td>90 (66.7%)</td>
<td>32</td>
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<tr>
<td>2014 Update</td>
<td>8 (29.6%)</td>
<td>19 (70.4%)</td>
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<td>(7/2010 – 6/2014)</td>
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<tr>
<td>Total</td>
<td>53 (32.7%)</td>
<td>109 (67.3%)</td>
<td>46</td>
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<thead>
<tr>
<th></th>
<th>Administrative</th>
<th>Case-by-Case Flexibility</th>
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<tr>
<td>Total</td>
<td>46</td>
<td>63</td>
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## Combined Analysis by Decade

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<tr>
<th>Orphan Drug Efficacy Evidence</th>
<th>Conventional</th>
<th>Total Flexibility</th>
<th>“Total Flexibility” Combination of:</th>
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<td></td>
<td></td>
<td></td>
<td>Administrative</td>
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<td></td>
<td></td>
<td></td>
<td>Case-by-Case Flexibility</td>
</tr>
<tr>
<td>Time Period</td>
<td>Conventional</td>
<td>Total Flexibility</td>
<td></td>
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<tr>
<td></td>
<td>7 (33.3%)</td>
<td>14 (66.7%)</td>
<td>5</td>
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<tr>
<td>1983* - 1989</td>
<td>14 (66.7%)</td>
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<tr>
<td>21 (35.6%)</td>
<td>38 (64.4%)</td>
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<tr>
<td>1990 – 1999</td>
<td>13 (26.5%)</td>
<td>36 (73.5%)</td>
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<tr>
<td>2000 – 2009</td>
<td>12 (37.5%)</td>
<td>21 (63.6%)</td>
<td>15</td>
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<tr>
<td>2010 – 2014**</td>
<td>53 (32.7%)</td>
<td>109 (67.3%)</td>
<td>46</td>
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<tr>
<td>Total</td>
<td>14 (66.7%)</td>
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<td>6</td>
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### Notes

* Beginning in January 1983, the date of enactment of the Orphan Drug Act.
** Through June 30, 2014.
Vimizim (elosulfase alfa) approved February ’14

– Single, randomized 24-week placebo-controlled trial of 176 patients with MPS IVA
– Patients were randomized 1:1:1 to Vimizim 2mg/kg every other week, every week, or placebo
– Only 1 of 2 investigational dose arms was positive on the primary endpoint, 6MWT, and FDA characterized the magnitude of this positive result as “modest,” questioning the clinically meaningfulness of the result
– In addition, the only other prespecified endpoint that measured a clinical outcome, 3MSC, did not approach statistical significance in either dose arm
– The FDA deputy office director stated the heterogeneity of the disease in presentation and progression makes it difficult to rely on a single endpoint that has clinical meaningfulness for all MPS IVA patients
Example of “Case-by-Case” Flexibility

May 1998 Guidance?
- The magnitude of the result on the 6MWT endpoint would likely not be viewed by FDA as “statistically very persuasive”
- Given the design and results, FDA likely would not have viewed it as unethical to conduct a second trial

FDAMA 115?
- There were no other clinical trials, nor other closely related pharmacological therapies that had been approved for this condition

Accelerated approval?
- FDA noted the “relationship between uKS levels and other measures of clinical response has not been established”
Conclusion

This update, together with the original 2012 analysis, highlight FDA continues to afford “extraordinarily reasonable flexibility” in its review of certain applications for orphan drugs.

Reinforces the need for FDA and drug companies to better understand and discuss potential areas for flexibility throughout the entire development process.
Part 2 –
Role of Patient Advocates in Drug Approval Process
Role of Patient Advocates in Drug Approval Process

- Pure Food & Drug Act (1902):
  - Nation’s 1st Law on Medicines
- FDASIA Law (2012) directs FDA
  - “to develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions”
- Took 110 years for Federal laws to recognize a role for those to be benefitted by medicines: patients!
  - Before 2012, the word “patient” never appeared in any Federal Drug Law
- 21st Century Cures Act’s section 3001 requires FDA to state the “patient experience data” submitted/reviewed as part of an NDA/BLA.
Role of Patient Advocate in Drug Approval Process

• A Patient Representative as part of FDA Review Team: Myozyme (2006) for Pompe disease
  - Ms. House is Chair of the International Pompe Association
  - As a Patient Representative, she was consultant to FDA Division of Neurology Products & ad hoc member of the Advisory Committee for Myozyme
  - After the Myozyme review, FDA medical reviewers have stated 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 defining clinically meaningfulness**

Ms. House speaking at FDA’s Inaugural Rare Disease Patient Advocacy Day on March 1, 2012
Role of Patient Advocates in Drug Approval Process

Duchenne Patient Community & the Approval of Exondys 51 (eteplirsen) for DMD

• Beginning in late 2014: Jett Foundation (JF) more systematically gathered experiences of patients and their caregivers over three years on drug
  – Semi-structured interviews
  – Rating scales
  – Additional videos

• July 2015: JF presented this information and video clips to CDER officials, including Drs. Woodcock, Moscicki, Jenkins, Unger, Dunn, and Farkas
  – FDA stated it would take patient experiences into account in review of an application
Role of Patient Advocates in Drug Approval Process

• April 25, 2015: PCNS Advisory Committee meeting for eteplirsen
  – JF provided a written report of findings to the committee (http://bit.ly/JFreport)
  – Christine McSherry of JF presents during “core” sponsor presentation, the first ever patient advocate to do so (https://youtu.be/-rtiH2oGwOo)
Role of Patient Advocates in Drug Approval Process

Example of parent-caregiver diary of son’s spontaneous collapses over course of trial:

*Began in Study 204 eteplirsen safety trial in mid-November 2014*
Role of Patient Advocates in Drug Approval Process

• What the Jett Foundation achieved
  – Provided semi-quantitative, qualitative, and video evidence about patients’ and caregivers’ experiences from before beginning therapy and while on drug
  – Highlighted an unexpected maintenance or increase in the ability of patients to participate in certain activities of daily living (ADLs)
  – Helped demonstrate clinical meaningfulness of eteplirsen’s clinical trial results
Role of Patient Advocates in Drug Approval Process

- Externally-led Patient-Focused Drug Development Meetings

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<thead>
<tr>
<th>Disease</th>
<th>Patient Organization</th>
<th>Date</th>
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<tbody>
<tr>
<td>Amyloidosis*</td>
<td>Amyloidosis Research Consortium</td>
<td>November 15, 2015 (prior to FDA guidelines)</td>
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<tr>
<td>Myotonic Dystrophy*</td>
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<tr>
<td>Acute Porphyrias</td>
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<td>Osteoarthritis</td>
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<td>March 8, 2017</td>
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<td>Spinal Muscular Atrophy*</td>
<td>Cure SMA</td>
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<td>Friedreich’s Ataxia (FA) *</td>
<td>FA Research Alliance</td>
<td>June 2, 2017</td>
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<td>Tuberous Sclerosis (&amp; LAM)*</td>
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<td>June 21, 2017</td>
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<tr>
<td>CG3, a rare kidney disease*</td>
<td>National Kidney Foundation</td>
<td>August 4, 2017</td>
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<tr>
<td>Lupus*</td>
<td>LFA, LADA, &amp; LRF</td>
<td>September 25, 2017</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>International Hyperhidrosis Society</td>
<td>November 13, 2017</td>
</tr>
</tbody>
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*Meetings my firm and I were involved with.
Role of Patient Advocates in Drug Approval Process

- Nov. 16th Approval of Genentech's hemophilia A treatment Hemlibra

![Patient Experience Data For Hemlibra](image)
Thank you
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