Regulatory Innovations in Neurological Disorder Therapies, including Spinraza and Exondys 51

ASENT 19th Annual Meeting
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Overview

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I. Role of Patient Advocates in Drug Approval Process

II. Reliance on Historically-Controlled Trials in Rare Diseases

III. Cumulative Distribution to Establish Clinical Meaningfulness

IV. Use of Accelerated Approval in Neurological Diseases

Part 1 –
Role of Patient Advocates in Drug Approval Process

I. Role of Patient Advocates in Drug Approval Process

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- 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.

1. Patient Experience Data

- 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 evaluating both safety and efficacy

Ms. House speaking at FDA's Inaugural Rare Disease Patient Advocacy Day on March 1, 2012

I. Role of Patient Advocates in Drug Approval Process

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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

II. 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)

II. Role of Patient Advocates in Drug Approval Process

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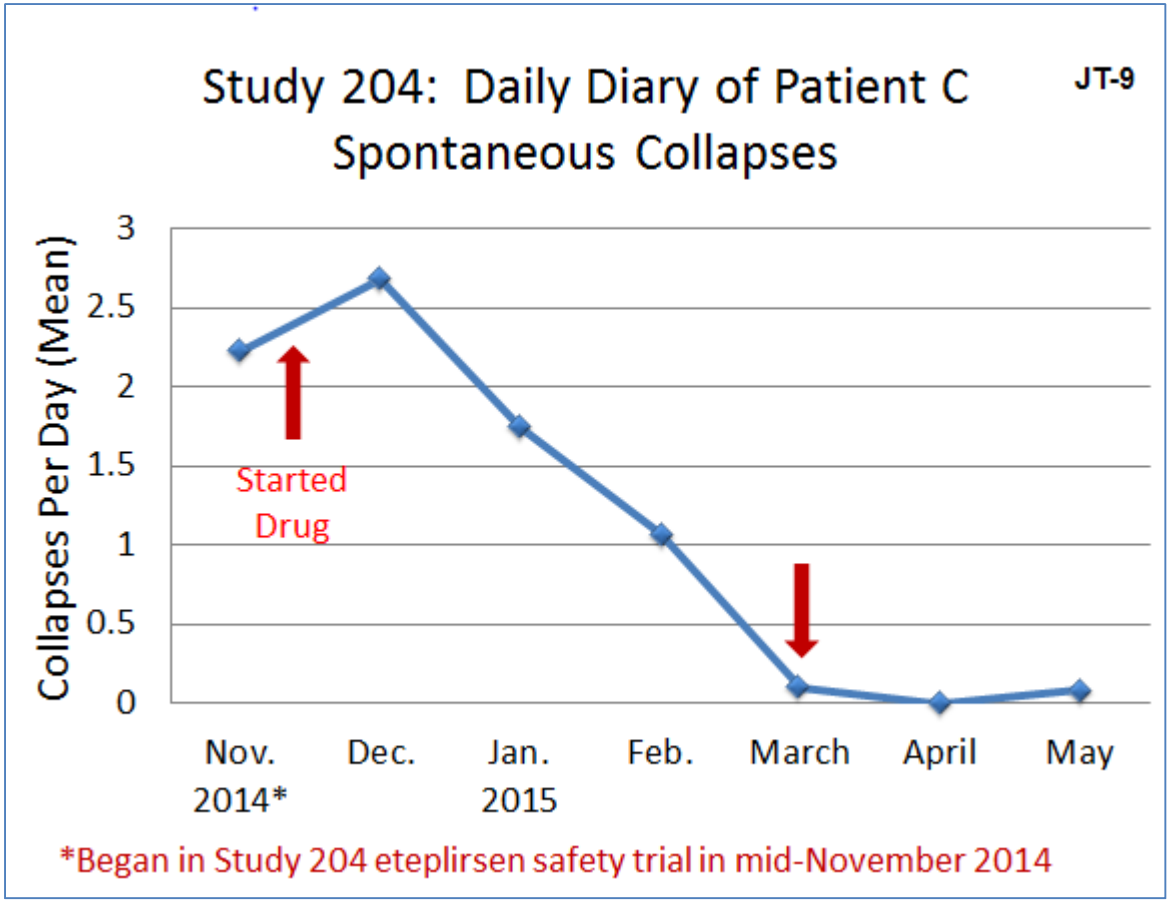
Example of parent-caregiver diary of son's spontaneous collapses over course of trial:



II. Role of Patient Advocates in Drug Approval Process

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- 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

Part 2 –
Reliance on Historically-Controlled Trials in Rare Diseases

II. Reliance on Historically-Controlled Trials in Rare Diseases

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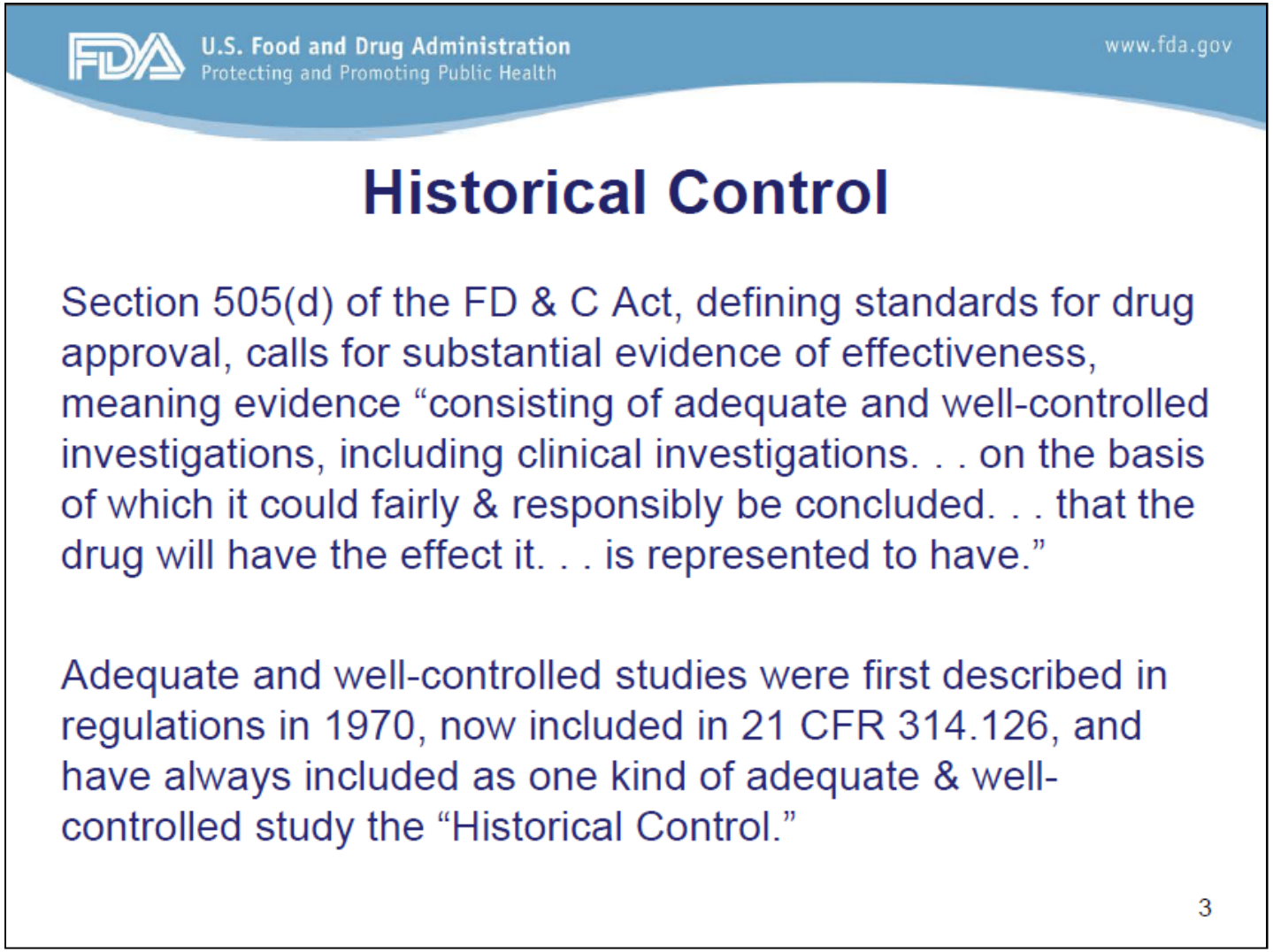

Source: Robert Temple, MD, PCNS AC Meeting, April 25, 2016

II. Reliance on Historically-Controlled Trials in Rare Diseases

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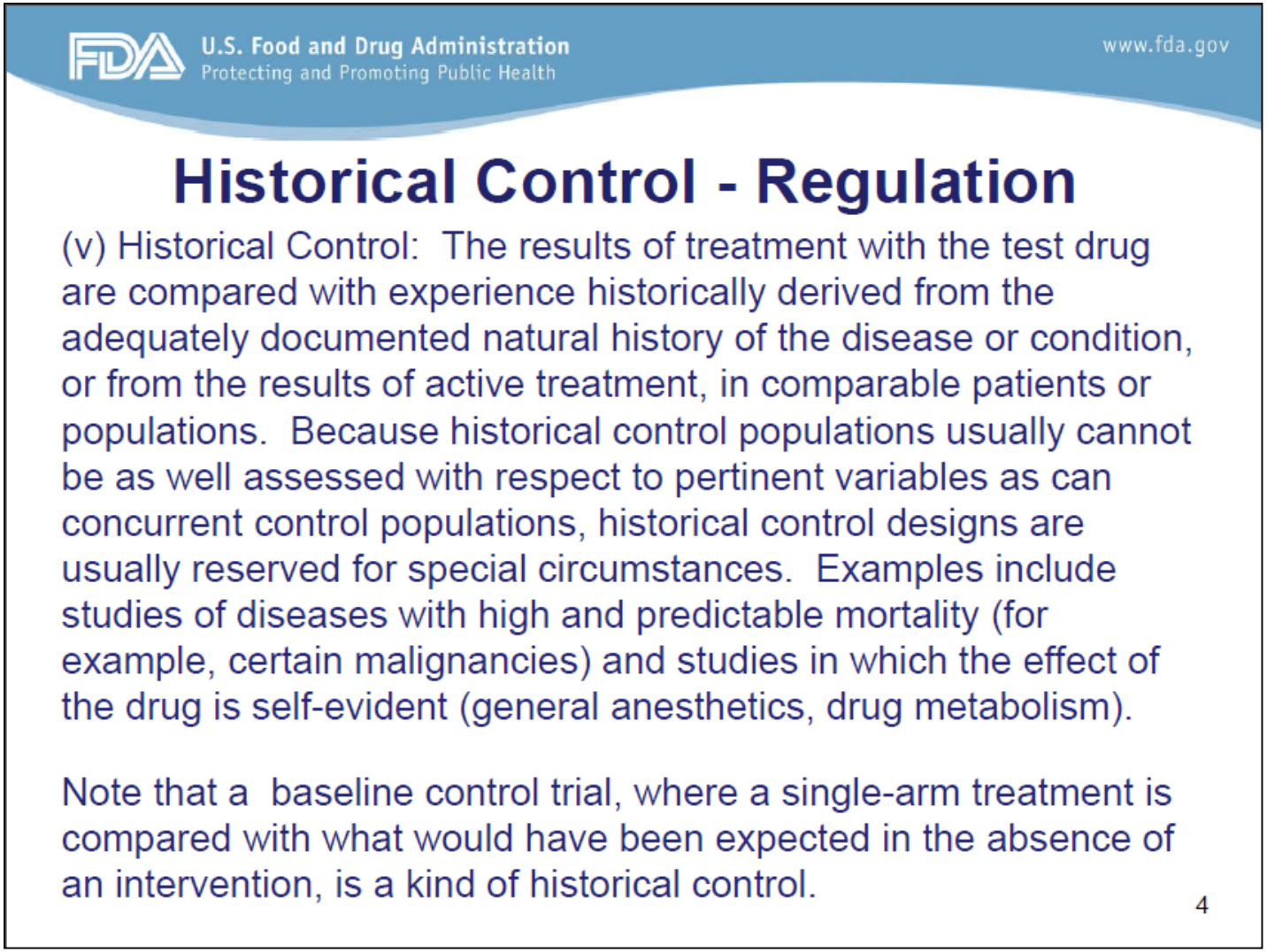

U.S. Food and Drug Administration
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Historical Control - Regulation

(v) Historical Control: The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

Note that a baseline control trial, where a single-arm treatment is compared with what would have been expected in the absence of an intervention, is a kind of historical control.

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Source: Robert Temple, MD, PCNS AC Meeting, April 25, 2016

II. Reliance on Historically-Controlled Trials in Rare Diseases

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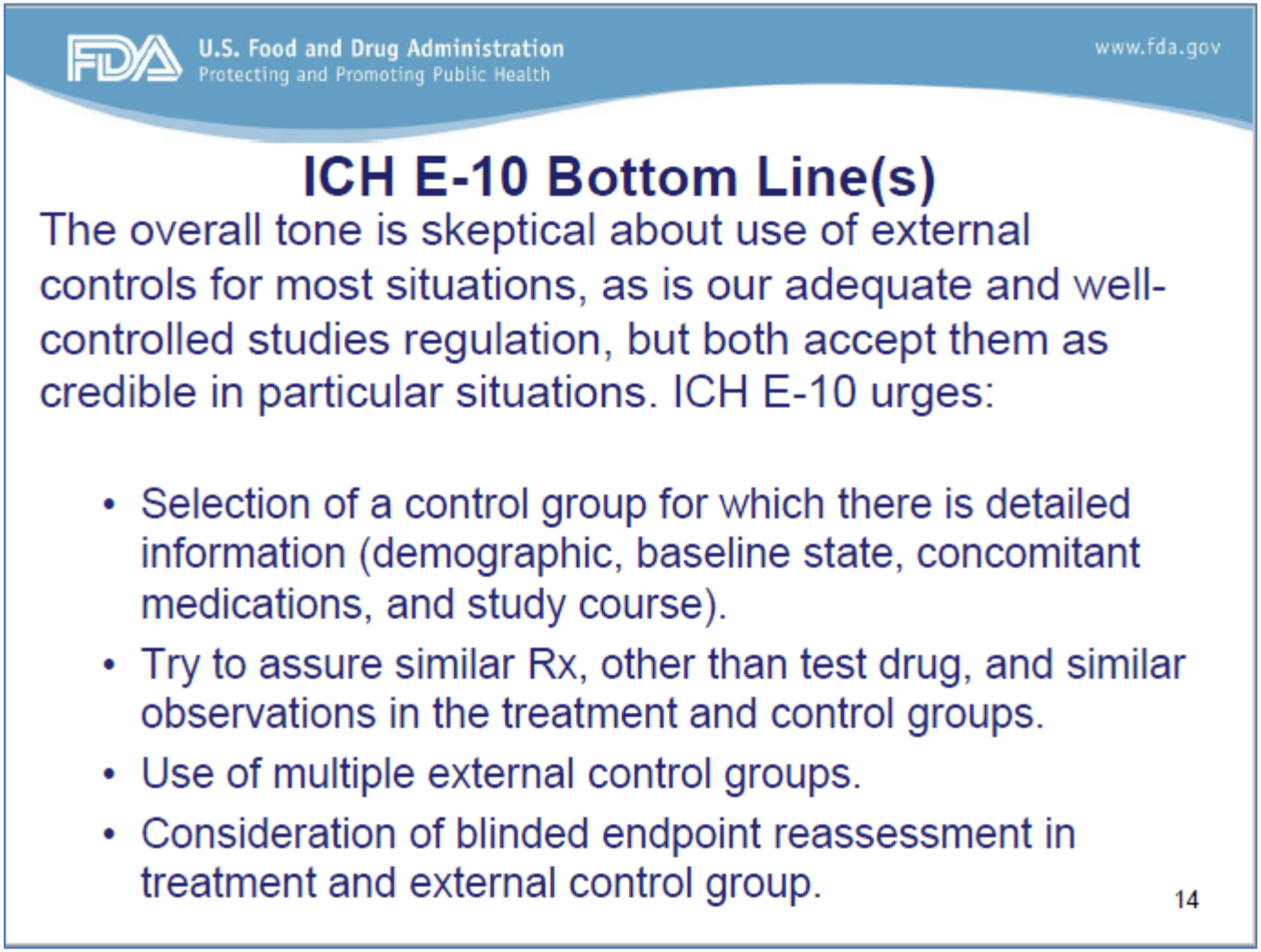

Source: Robert Temple, MD, PCNS AC Meeting, April 25, 2016

II. Reliance on Historically-Controlled Trials in Rare Diseases

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ICH E-10 Bottom Line(s) (cont)

ICH E-10 also suggests that the main credible use of external controls is when there is an ethical difficulty in doing the RCT. The suggested remedy is to randomize the earliest studies: "The concurrently controlled trial can detect extreme effects very rapidly and, in addition, can detect modest, but still valuable, effects that would not be credibly demonstrated by an externally controlled trial."

ICH E-10 again notes that external control trials are most likely to be persuasive when the effect is very large.

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Source: Robert Temple, MD, PCNS AC Meeting, April 25, 2016

II. Reliance on Historically-Controlled Trials in Rare Diseases

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Historically-Controlled Trial of Eteplirsen:

- Study 202 consisted of all patients in Study 201, which were switched to active drug, and were continued to be followed on 6MWT, timed 10-meter run, NSAA, and rise time (n=12)
- Comparison to an external control group obtained from 2 registries in Italy and Belgium (n=13 matching including exon 51; n=50 matching for any exon)
- Matching between treatment and on prognostic factors: (1) baseline age, (2) baseline weight, (3) length of steroid use, (4) baseline 6MWT
- At AdComm, the FDA reviewer raised questions of comparability between study patients and patients in the registries
  - Imbalances in baseline NSAA scores & initial age of steroid use
  - Other unknown (and unspecified) prognostic factors
- Sponsor noted an imbalance biasing against treatment arm on variables that FDA thought were key: dose of steroids used and amount of physical therapy

II. Reliance on Historically-Controlled Trials in Rare Diseases

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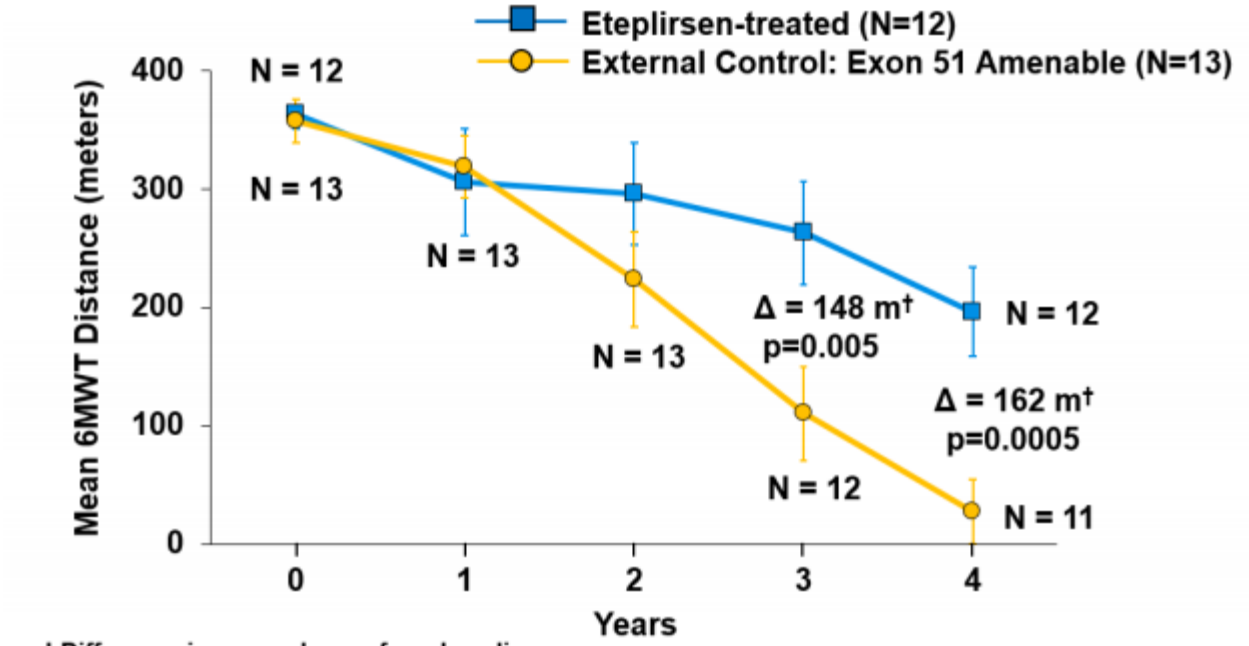
Historically-Controlled Trial of Eteplirsen (cont.):

- To account for matching across prognostic factors, the data was presented by Sarepta as time-on-treatment

Figure 2: Mean 6MWT Values Over time in Eteplirsen Treated Patients vs External Control Amenable to Exon 51 Skipping



† Difference in mean change from baseline
Patients who lost ambulation contributed a score of 0 to the mean
1 EC Subject was missing data at Year 3 & 4, 1 EC Subject was missing data at Year 4 only

Source: Sarepta, PCNSD Advisory Committee Meeting Briefing Document at 21.

Historically-Controlled Trial of Eteplirsen (cont.):

- In its review, the FDA review division concluded that there was not a clear separation of the disease course between eteplirsen-treated patients and external controls
- In presenting its analysis, FDA displayed the data as a function of age, accounting for just one prognostic factor

II. Reliance on Historically-Controlled Trials in Rare Diseases

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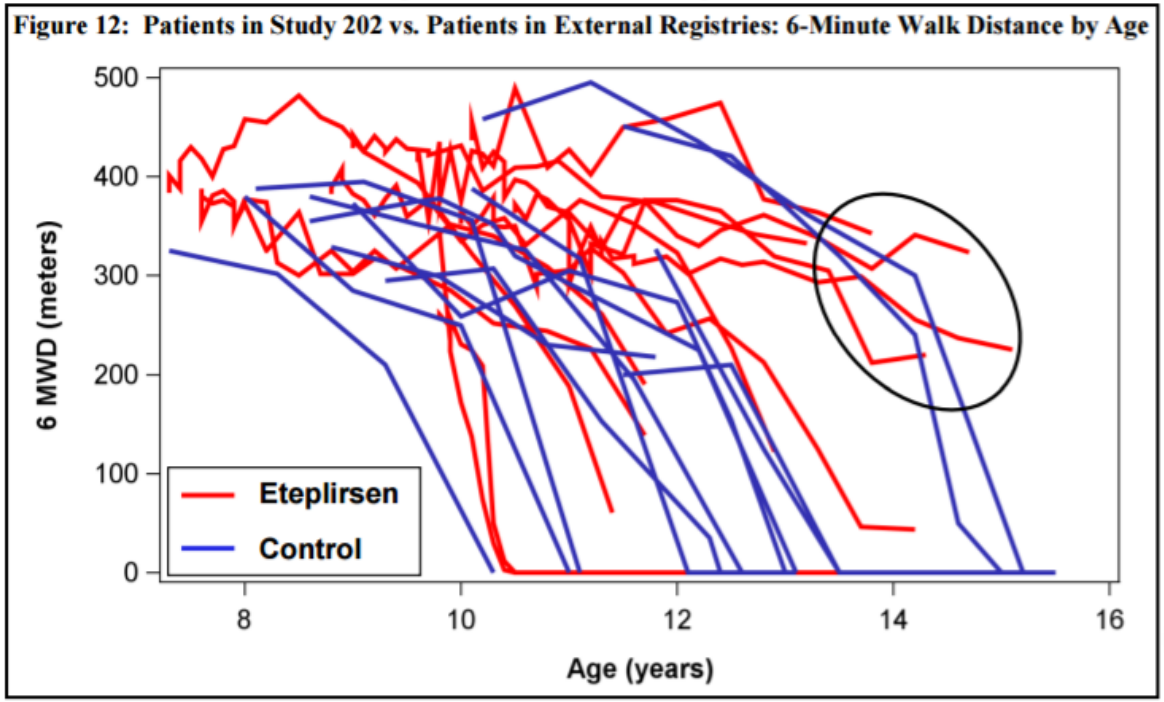
Historically-Controlled Trial of Eteplirsen (cont.):



"…by simple visual inspection, the two groups show little difference in performance."

Source: Ellis Unger, MD, Office Director Decisional Memo (July 17, 2016) at 32-33

II. Reliance on Historically-Controlled Trials in Rare Diseases

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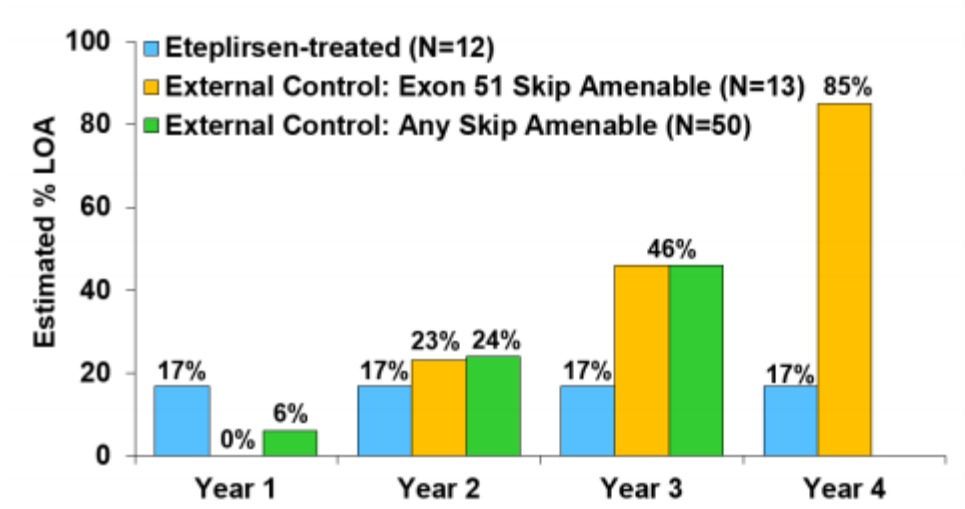
Historically-Controlled Trial of Eteplirsen (cont.):

- Sarepta also provided a historically-controlled analysis of loss of ambulation:

Figure 4: Kaplan-Meier Estimates of Loss of Ambulation Over 4 Years in Eteplirsen-Treated Patients vs. Primary External Control (N=13) and Over 3 Years vs. Secondary External Control



Eteplirsen's treatment benefit on the delay of DMD progression as measured by the 6MWT is further confirmed by a reduction in the risk of Loss of Ambulation over a 4-year time period when compared to the external control group amenable to exon 51 skipping (17% vs 85%). This difference is accompanied by a statistically persuasive p-value of 0.011.

Source: Sarepta, PCNSD Advisory Committee Meeting Briefing Document at 23.

II. Reliance on Historically-Controlled Trials in Rare Diseases

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Part 3 –
Cumulative Distribution to Establish Clinical Meaningfulness

III. Cumulative Distribution to Establish Clinical Meaningfulness

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- FDA approval of Ionis/Biogen's Spinraza (nusinersen) the first treatment for Spinal Muscular Atrophy (Dec. 23, 2016)
  - ENDEAR trial: sham-controlled clinical study in infantile-onset SMA patients (planned interim analysis at 6 months)
    - Treated patients (n=52) achieved and sustained important motor milestones (Section 2 of Hammersmith Infant Neurologic Exam) compared to untreated patients (n=30) (40% vs. 0%, $p<0.0001$)
  - Open-label studies in SMA Types 1, 2, and 3 patients:
    - Achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so
    - Maintained milestones at ages when they would be expected to be lost
    - Survived to ages unexpected
  - Approved within **three months** of receipt of application by FDA
  - Fastest approval in history of FDA for any therapy outside of cancer and AIDS

III. Cumulative Distribution to Establish Clinical Meaningfulness

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- FDA approval of Ionis/Biogen's Spinraza (nusinersen) the first treatment for Spinal Muscular Atrophy (Dec. 23, 2016)

Table 2. Motor Milestone Response and CHOP-INTEND Results

Endpoint	SPINRAZA-treated patients (n=52)[1]	Sham-control patients (n=30)[1]
Motor Milestone (HINE Section 2)		
Achievement of a motor milestone response	21 (40%) p<0.0001	0 (0%)
CHOP-INTEND Improvement from Baseline[2]		
At least 4-points	33 (63%)	1 (3%)
CHOP-INTEND Worsening from Baseline[2]		
At least 4-points	2 (4%)	12 (40%)

[1]Analyses included all subjects who were alive with the opportunity for at least a 6-month (Day 183) assessment and all subjects who died or withdrew from the study at the time of the interim analysis

[2]Not statistically controlled for multiple comparisons at interim analysis

III. Cumulative Distribution to Establish Clinical Meaningfulness

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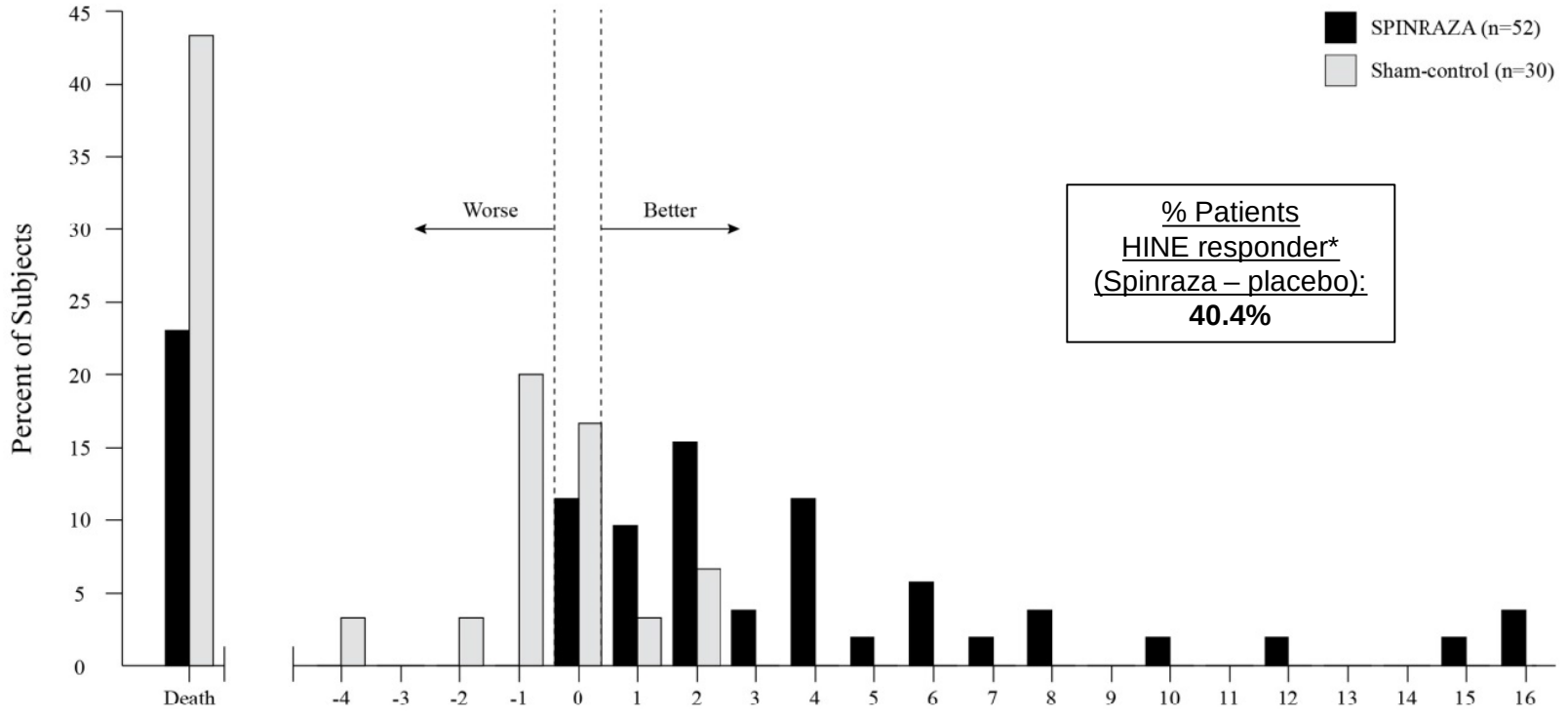
- Spinraza (nusinersen) example of cumulative distribution

Figure 1. Net Change from Baseline in Total Motor Milestone Score (HINE) by Percent of Subjects in the Interim Efficacy Set*



III. Cumulative Distribution to Establish Clinical Meaningfulness

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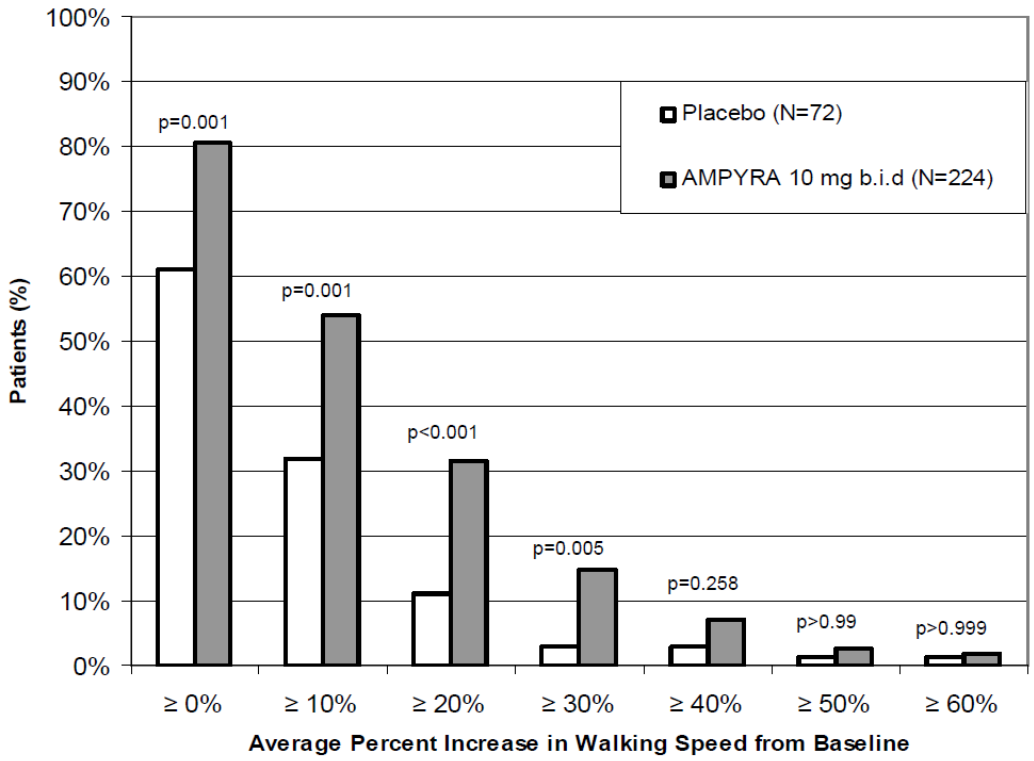
- Other examples of cumulative distribution: Ampyra for MS (2010)

Figure 1: Average walking speed change (%) from baseline during the double-blind phase of Trial 1



P values provided at each threshold comparing AMPYRA to placebo.

Mean Change in Walking Speed:
Ampyra **2.37 ft/sec**
vs
Placebo **2.30 ft/sec**

III. Cumulative Distribution to Establish Clinical Meaningfulness

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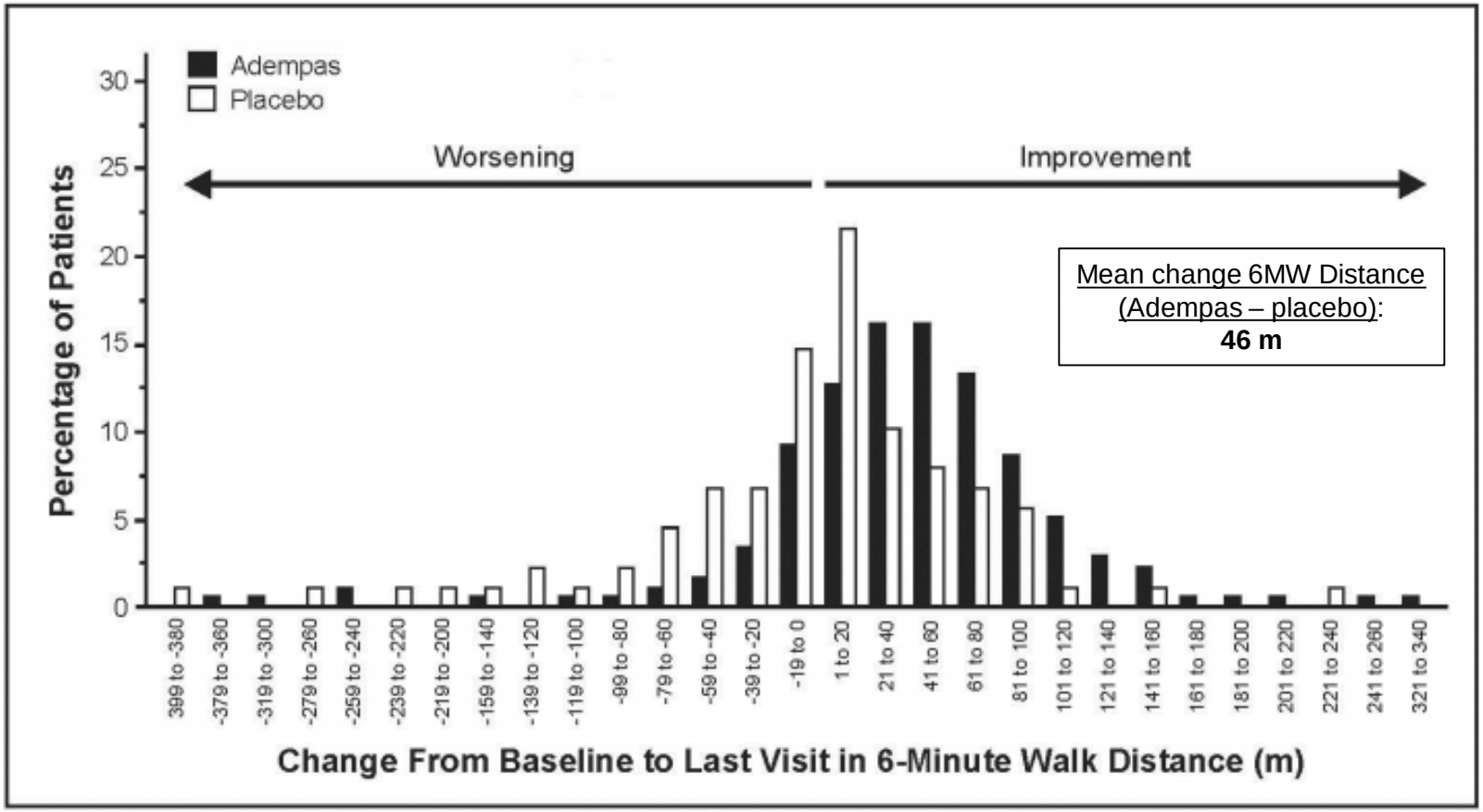
- Other examples of cumulative distribution: Adempas for PAH (2003)

Figure 4: CHEST-1 Distribution of Patients by Change from Baseline in 6-Minute Walk Distance



Part 4 –
Use of Accelerated Approval in Neurological Diseases

IV. Use of Accelerated Approval in Neurological Diseases

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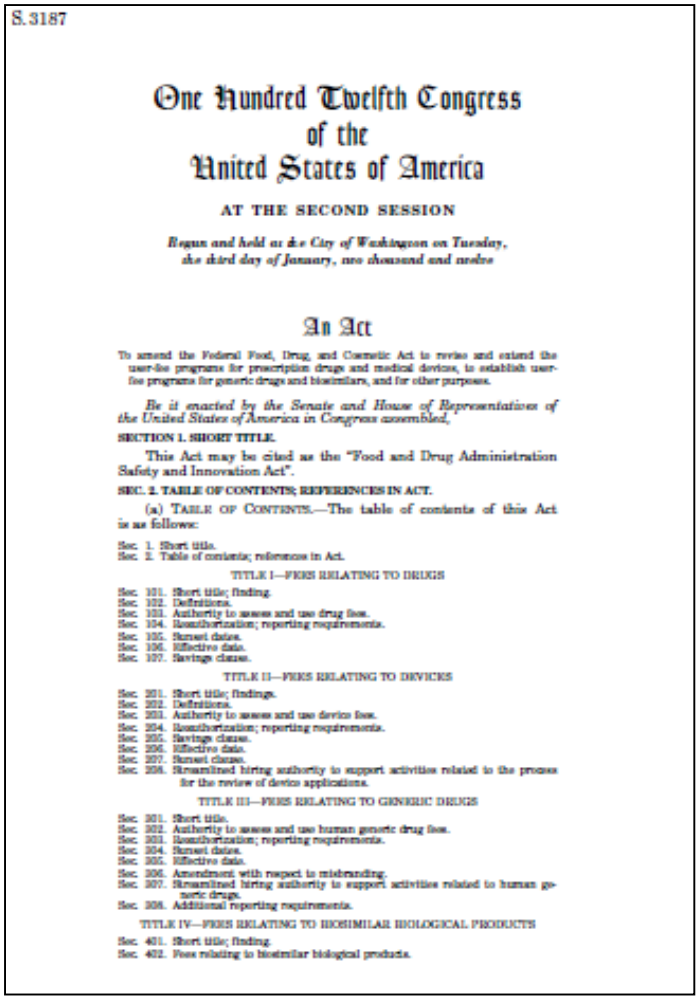
- Originally created by FDA for AIDS crisis in 1980's
- Program was placed into statute in the FDA Safety and Innovation Act (FDASIA) in July 2012



S. 3187

One Hundred Twelfth Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Tuesday, the third day of January, two thousand and twelve

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, to establish user-fee programs for generic drugs and biosimilars, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Safety and Innovation Act".

SEC. 2. TABLE OF CONTENTS; REFERENCES IN ACT.

(a) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

IV. Use of Accelerated Approval in Neurological Diseases

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- In July 2012, FDASIA defined an Accelerated Approval 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."

- FDA has utilized Subpart H in 21 approvals for conditions other than HIV/AIDS or cancer.

- FDA's first non-HIV, non-cancer Subpart H approval was in 1993! Betaseron for multiple sclerosis (MS).

IV. Use of Accelerated Approval in Neurological Diseases

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- Subpart H approval of Exondys 51 (eteplirsen) for DMD:
  - Dr. Woodcock and Dr. Unger, as well as the review team, agree that eteplirsen in RCT produces statistically significant increases in dystrophin compared to control
  - However, did not reach levels seen in Becker muscular dystrophy (an extrapolation)
  - Dr. Woodcock found "no rational basis for identifying a specific threshold value for dystrophin values that would be needed to support a determination that a particular level is 'reasonably likely' to predict clinical benefit"
  - She found that higher levels of dystrophin are associated with greater function using a "totality of evidence" approach

Source: Robert Califf, MD, Commissioner's Decision (Sept. 16, 2016) at 2-5

Inaugural Hearing on 21st Century Cures: May 20, 2014

Energy & Commerce Subcommittee on Health

– Frank Sasinowski's testimony at this 1st hearing focused on expanding use of Subpart H/Accelerated Approval pathway and importance of including patient voice in FDA regulatory processes

IV. Use of Accelerated Approval in Neurological Diseases

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- The 21st Century Cures Act's section 3033 creates process and requirements for designating a drug as a RAT
  - Noteworthy effect of designation: ***eligible for accelerated approval*** under **current** FDA preapproval standards but with **new postapproval requirements**
  - Therefore, RAT is an opportunity to increase the visibility and use of accelerated approval as it is one visible sign of movement to expand use of accelerated approval beyond cancer and AIDS
- Section 3034 - requires FDA to issue guidance within 1 year
- Section 3035 - requires HHS to report annually to Congress the ***number of applications granted accelerated approval***

IV. Use of Accelerated Approval in Neurological Diseases

Rare Disease Congressional Caucus Briefing: Advancing Rare Disease Treatments in the Era of Cures and Health Care Reform

March 2, 2017

- Opportunities for RAT:
  - Technical amendment to explicitly include gene therapies in definition of RAT
  - In PDUFA 6, expand this designation and its benefits (e.g., relaxing postapproval requirements under accelerated approval) to other innovative categories of therapies (such as anti-sense oligonucleotides or ASO therapies, e.g., Spinraza approved Dec. 23, 2016 for spinal muscular atrophy, including “floppy babies”).