

# Three Thoughts on Regulating Therapies for Americans with Rare Diseases

FDA Workshop – Promoting Effective Drug Development Programs:  
Opportunities and Priorities for FDA’s Office of New Drugs (OND)

FDA White Oak Campus

November 7, 2019

Frank J. Sasinowski , M.S., M.P.H., J.D.

*Vice Chair, EveryLife Foundation for Rare Diseases*

*Adjunct Professor of Neurology, U. of Rochester Medical School*

*Director, Hyman, Phelps & McNamara, P.C.*

# Three Thoughts on Regulating Therapies for Americans with Rare Diseases

1. Expanding use of external controls
2. Promoting intra-OND consistency
3. Articulating the actual quantum of effectiveness required

# 1. Expanding Use of External Controls: Natural History (NH), Patients-As-Own-Control (PAOC) and “Hybrid Controls”

*Why rely upon just one control when up to 3 controls are possible?*

- In every rare disease, key biological understandings will remain beyond current scientific reach.
- Randomizing subjects in any small trial may result in Type 1 or Type 2 error simply because a key prognostic variable that would predict which persons will progress more rapidly and which more slowly is not yet recognized.

*What are we “looking for” in these types of historical controls?*

- For PAOC, look to see whether those randomized to placebo act as they did before randomization and look to see whether there is an inflection point (a divergence) that occurs in the pattern at the time of randomization for those randomized to the investigational arm.
- For NH, compare both placebo and drug arms to their matched NH controls and see if there is a concordance between NH and those randomized to placebo and divergence between NH and those on drug.

# 1. Expanding Use of External Controls: Frank's Rule

## Frank's Rule:

- ❖ All studies of rare diseases should **always try** to include **both** of the following:
  1. Secure as much clinical and biomarker information on each subject before baseline to use for analyzing patients as their own control.
  2. Have a NH control.
    - a. Use prospective or retrospective NH as external historical controls.
      - i. Use variety of methods to match on prognostic variables (e.g., best match, best three matches, virtual matching) to look for concordance among the various methods of matching.
    - and/or
    - b. Use NH to add subjects to concurrent control arm.
      - i. This expanded concurrent control arm may be referred to as a “hybrid control”.

## Frank's Rule is consistent with FDA regulations:

- ❖ Historical controls can meet requirements for an adequate & well-controlled study. 21 CFR 314.126(b)(2)(v)

# 1. Expanding Use of External Controls:

## OND Use of NH & PAOC Across OND Divisions

- March 2019 Guidance on Rare Diseases: Natural History Studies for Drug Development (draft).
- Senior FDA officials have cited Brineura to illustrate OND reliance on a retrospective NH (RNH) control.
- Some OND Divisions have relied upon NH controls in approval decisions.

<b>Drug (recent examples)</b>	<b>Indication</b>	<b>Division</b>	<b>External Control</b>
Cholbam (2015)	Bile acid synthesis disorders; peroxisomal disorders	DGIEP	PAOC
Xuriden (2015)	Hereditary orotic aciduria	DGIEP	PAOC
Strensiq (2015)	Infantile- and juvenile-onset hypophosphatasia	DGIEP	RNH
Kanuma (2015)	Lysosomal acid lipase deficiency	DGIEP	RNH
Brineura (2017)	Late infantile neuronal ceroid lipofucinosi s type 2	DGIEP	RNH
Exondys 51 (2016)	Duchenne muscular dystrophy	DNP	RNH
Crysvita (2018)	X-linked hypophosphatemia	DBRUP	RNH
Gamifant (2018)	Primary hemophagocytic lymphohistiocytosis	DHP	PAOC
Egaten (2019)	Fascioliasis	DAIP	NH

## 2. Promoting Intra-OND Consistency on Rare Diseases

- Advancement of treatments for rare diseases requires that we not allow the unique features and considerations of each rare disease to prevent us from identifying commonalities that allow us to treat similar situations similarly.
  - FDA Public Workshop in May 2019 on “Bridging the Commonalities” aimed to understand commonalities across rare diseases with regards to drug development challenges and patient perspectives.
- At the October 2019 NORD Summit, Dr. Woodcock described the new Division of Rare Diseases and Medical Genetics (DRDMG) as a virtual “Center of Excellence for Rare Diseases” (RDCE) in that DRDMG will be the OND thought leader for rare diseases in all areas outside of neurology and oncology.

## 2. Promoting Intra-OND Consistency on Rare Diseases

- Opportunities for advancing consistency include learnings from Dr. Pazdur & Oncology Center of Excellence (OCE).
  - Have a dedicated medical officer in every OND Review Division that has experience with and is passionate about rare diseases and who is accountable to understand: 1) the science of small trials and 2) the exercise of scientific judgment across OND Divisions for rare diseases. Consider an Associate Director of Rare Diseases for each OND Review Division (akin to the Associate Director for Safety or for Labeling). Dr. Padzur asked for volunteers for novel OCE posts.
  - Have designated reviewer who is an expert on science of small trials housed within each Division & would be key consult during review of every rare disease therapy in that Division.
  - Given the prevalence of therapies in development for rare diseases, require (rather than merely voluntary) training on rare diseases for OND Reviewers (and CDER statisticians).

# 3. Articulating Quantum of Effectiveness Required for Rare Diseases

- On Sept. 6, 2019, at EveryLife Foundation 11<sup>th</sup> Annual Scientific Workshop, OND's Director, Dr. Peter Stein, made the first public FDA statement on what constitutes "confirmatory evidence" under the FDAMA 115 single trial standard.

## Single trial plus confirmatory evidence: types of evidence



*Single A&WC clinical trial supported by:*

- **Results from trials in a related indication**
  - FDA may accept one trial in a related indication (i.e., similar drug MOA in producing clinical benefit)
- **Compelling mechanistic information from earlier clinical or non-clinical studies**
  - Reliance on pharmacodynamic endpoint with well-established relationship to clinical endpoint
  - Reliance on well-established, translatable animal model
- **Well described natural history of disease**
  - Evidence clearly describing natural history of disease: may be natural history study, registry, compelling case series
- **Adequate and well controlled trials from other members of same drug class**
  - Same pharmacological target

# 3. Articulating Quantum of Effectiveness Required for Rare Diseases

- ❖ FDA's description of responsibilities for assessing effectiveness of orphan drugs:
  - Traditional description (1980's thru late '90's): Orphan Drug Act (ODA) did not amend 1962 law's substantial evidence of effectiveness standard (full stop).
  - Current description: While ODA did not amend 1962 law, FDA recognizes two types of situations in which a single study may meet the standard: 1) a statistically highly persuasive (p value of at least less than 0.01) single study as per FDA's May 1998 guidance, or 2) a single study of conventional statistical significance (p value of less than 0.05) but with "confirmatory evidence" as per FDAMA 115.
- Frank's view: FDA's practice has been to apply even more "flexibility" than that presented in the 1997 FDAMA alternative standard and in the FDA's 1998 guidance.
- FDA has long had the authority to exercise such "flexibility" and has historically applied such flexibility. (see 21 CFR 314.105)

# 3. Articulating Quantum of Effectiveness Required for Rare Diseases: *Option 1*

❖ To justify the 1/3 of orphan drug approvals\* that do not meet either the 1962 standard or either of the single study exceptions (under the 1997 FDAMA standard or 1998 Evidence Guidance), there needs to be a new way of describing and communicating FDA's authority to act on drugs for rare diseases. Consider the following as a proposed new EXECUTIVE SUMMARY OF SUCH A STATEMENT (& see next slide for alternative statement):

- The 1962 law established a standard that FDA has interpreted as usually requiring 2 adequate and well-controlled (A+WC) positive trials.
- In 1997 this was amended to allow, in the alternative, for a single A+WC study with confirmatory evidence. FDA's 1998 Evidence Guidance described another single study approval pathway.
- Yet, FDA's practice has been to apply even more "flexibility" than that presented in the 1997 alternative standard or in the FDA's 1998 guidance.
- FDA has long had the authority to exercise such "flexibility". (see 21 CFR 314.105).
- FDA has historically applied such flexibility\* on a "case-by-case" basis.

\*See Sasinowski 2012 & 2015 papers on Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs

# 3. Articulating Quantum of Effectiveness Required for Rare Diseases: Option 2

Current Statement: Even though the ODA did not amend 1962 law, a single positive A+WC study may meet the statutory standard if it is EITHER:

- a. Highly statistically persuasive (p value of at least less than 0.01) study with no other evidence of effectiveness as per May 1998 guidance, OR
- b. Conventionally positive (p value less than 0.05) study with some form of confirmatory evidence (note: there is growing recognition of this alternative standard).

**Proposed Statement: In addition, the Agency has long-established authority that “demands flexibility in applying the [statutory (1962 and 1997) and administrative (1998)] standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information for a particular drug to meet the statutory [and administrative] standards.” 21 CFR 314.104(c).**

**As such, FDA is compelled to exercise its scientific judgment on a case-by-case basis in reviewing each therapy being investigated for a rare disease. That exercise of judgment can be affected by many factors, including among others, the rarity and severity of the condition and the relative availability of other satisfactory therapies.**

# Thank you!

Frank J. Sasinowski , M.S., M.P.H., J.D.

[fjs@hpm.com](mailto:fjs@hpm.com)