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Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014

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Abstract

Background: This study serves as a follow-up to a March 2012 analysis conducted by Frank Sasinowski that reviewed the quantum of effectiveness evidence that is required to secure FDA approval of therapies for rare diseases, or orphan drugs, from the 1983 enactment of the Orphan Drug Act through June 30, 2010. The current study was designed to determine, over the 4 years since the original study, how frequently FDA has required marketing applications of drugs for rare diseases to provide the conventional level of proof of effectiveness that is ordinarily expected for most drugs for prevalent diseases. *Methods:* This study employed methods similar to the original analysis, identifying the noncancer orphan drugs approved as new chemical entities by relying on FDA's publicly available documents for drugs approved by FDA from July 1, 2010, to June 30, 2014. These materials were used to identify the basis for each drug's approval, and each approval was analyzed and classified. *Results:* The results of this study show that for just over two-thirds of all noncancer orphan drugs approved between July 1, 2010, and June 30, 2014, FDA did not require the orphan drug applications to provide the conventional level of proof of effectiveness that is ordinarily expected for drugs for prevalent diseases. This is consistent with the results of the 2012 analysis. *Conclusions*: The findings further support that FDA has demonstrated extraordinarily reasonable flexibility in its review of certain applications for orphan drugs and reinforce the need for FDA and drug companies to better understand and discuss the various types of flexibility.

Keywords

rare disease, orphan drug, FDA, drug approval, effectiveness, flexibility

Introduction

There are an estimated 7000 diseases that each affects a small number of patients, and approximately 300 of these diseases have medicines approved to treat the patients with that rare disorder. This therapeutic disparity between the number of known "rare" diseases and those that have an approved treatment continues to a yawning gap for which there is great concern.[1] This gap represents a huge unmet medical need for those with rare, "orphan" diseases, which are diseases that affect 200,000 or fewer patients in the United States.[2] In an attempt to address a concern that medicines were not being developed for these diseases that affect small numbers of patients, the Orphan Drug Act of 1983 was enacted.[3] This law created financial incentives for drug companies to develop therapies for rare diseases, also known as orphan drugs.

This law, however, did not amend or revise the statutory standards in the Federal Food, Drug, and Cosmetic Act for establishing that a new drug is safe and effective for its proposed use. In other words, the standard of approval for orphan drugs is legally the same as the standard of approval for all other drugs. Since 1962, the standard has been that for the US Food and Drug Administration (FDA) to approve a new drug, there must be "substantial evidence" of effectiveness derived from "adequate and well-controlled investigations."[4] While not amended by the 1983 law, this language does provide FDA medical reviewers and officials with flexibility to

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determine what constitutes "substantial evidence" of a drug's effectiveness, that is to say, whether adequate information exists for FDA to conclude that the proposed treatment actually benefits the patients with that disease or condition.

Exploring the level of flexibility that FDA has exercised in applying this standard in FDA's approval of orphan drugs, in March 2012, an analysis conducted by Frank Sasinowski, one of the coauthors of this article, reviewed the quantum of effectiveness evidence that has been required to secure FDA approval of orphan drugs from the 1983 enactment of the Orphan Drug Act through June 30, 2010.[5] The study closely examined how much flexibility FDA exercised in its review and approval of these orphan drugs.[i] Sasinowski's 2012 analysis of available orphan drug precedents established that FDA had exercised meaningful and reasonable flexibility in its review and regulatory actions on therapies for rare disorders. This article extends that earlier seminal analysis by presenting the results of a similar type of analysis to those orphan drugs approved between July 1, 2010, and June 30, 2014.

Purpose of This Study

Sasinowski[5] found that FDA exercised some form of flexibility in the approval of two-thirds of the 135 noncancer orphan therapies approved as new chemical entities from the enactment of the Orphan Drug Act in 1983 through June 30, 2010. The current study serves as a follow-up to Sasinowski, designed to determine whether, over 4 years from 2010 to 2014, FDA has required orphan drug applications to provide the conventional level of proof of effectiveness that is ordinarily expected for most drugs for prevalent diseases. These issues remain critical as the proportion of new molecular entities that reach the market via a rare disease indication is growing.[6] At the same time, there are nearly 7000 rare diseases that affect about 30 million Americans, yet there are approximately 300 treatments currently available.[7] Meanwhile, many of the challenges of studying drugs in rare disease patient populations continue to exist, which results in high development costs and high failure rates.[7] This study examines whether, for orphan drugs approved from July 2010 through June 2014, FDA continued to exercise the flexibility that had been reported in the Sasinowski paper for therapies approved prior to July 2010. This study also illustrates the nature and scope of any such flexibility.

Methods

To allow comparison to previous orphan drug approvals, this study employed similar methods to Sasinowski,[5] identifying 27 noncancer orphan drugs approved as new chemical entities.[ii] Orphan drug approvals were identified by referring to FDA publicly available lists of therapies approved by FDA from July 1, 2010, to June 30, 2014, and FDA's listing of therapies designated as orphan drugs. As was done in the analysis in Sasinowski, therapies for rare cancers were excluded from this analysis. Senior FDA drug officials had advised that the approvals of therapies for rare cancers not be included since the regulatory pathway for these is generally unique to cancer therapies. Aside from excluding therapies for rare cancers, the scope of this analysis is broad, consisting of both NDAs and BLAs as well as those therapies reviewed in the Center for Biologics Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

For each approved drug, access was sought from Drugs@FDA and the FDA.gov website for the FDA approval letter, the labeling at the time of approval, the decision memoranda of the FDA officials involved in the approval of the therapies, and the reviews of the FDA medical and statistical officers. These documents were used to identify the basis for each drug's approval and were analyzed and classified, in our judgment, as to whether or not the quantum of effectiveness evidence would have met the usual and traditional showings of effectiveness that would ordinarily be expected for a common or prevalent disorder. For those orphan drugs that did not fall within this classification because their approval was based on some exercise of FDA flexibility, further analysis subdivided those drugs into either those whose approvals were based on a formal, expressed FDA system for flexibility (administrative flexibility) or those whose approvals were not based on any such formal FDA expression of flexibility (case-by-case flexibility).

In summary, this article classifies the 27 orphan drug approvals into 1 of 3 categories based on an analysis of the quantum of effectiveness evidence:

1. "conventional" quantum of evidence,
2. evidence consistent with a formal FDA system for exercising discretion or "administrative flexibility," or
3. evidence that is consistent with a "case-by-case flexibility."

The first 2 of these classifications are described in the following, and the third classification is one by exclusion. This third classification is somewhat akin to a clinical diagnosis that is arrived at only by excluding all other possibilities. That is how we classified a therapy as one of "case-by-case flexibility." In other words, if we classified a therapy as being an example of "case-by-case flexibility," it means that we, after carefully reviewing the available effectiveness evidence, concluded that the evidence did not consist of 2 adequate and well-controlled "positive" studies, nor did the evidence fit (1) FDAMA 115 or the May 1998 Evidence Guidance (see "Single-Study Approval Authorities" in the following section)

or (2) accelerated approval (see "Accelerated Approval/Fast Track/Subpart H" in the following section).

Conventional Showing of Effectiveness

The "conventional" classification is for those orphan drugs whose quantum of effectiveness evidence would satisfy the usual and traditional showing of effectiveness. The 1962 Amendments to the FDC Act added the requirement that for FDA to approve commercial marketing of any drug, it had to conclude that there exists "substantial evidence . . . consisting of adequate and well-controlled investigations, including clinical investigations," such that "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" could "fairly and responsibly" conclude that the drug will have the effects that the drug purports or claims to have in the sponsor's proposed labeling for that therapy.[8] FDA has interpreted this standard to mean, generally, a minimum of 2 such adequate and well-controlled clinical studies. FDA has promulgated regulations defining the types of trial designs that are "adequate and well-controlled studies."[9] Traditionally, FDA has accepted 2 adequate and well-controlled trials when each meets its primary endpoint by its prespecified primary analysis and is statistically significant (a P value of $\leq .05$).

Administrative Flexibility

The "administrative flexibility" classification is for the approvals that rely on an exercise of administration discretion whose source is found in a formal FDA statute (FDAMA 115, Fast Track), regulation (Subpart H), or guidance (May 1998 Evidence Guidance). Within this "administrative flexibility" classification, there are 2 different ways that the flexibility is manifest: either affecting the number of studies required (see "Single-Study Approval Authorities" section) or by affecting the type of effectiveness evidence required (see "Accelerated Approval" section).

Single-Study Approval Authorities

There are 2 different formal single-study approval authorities that satisfy the FDC Act's substantial evidence of effectiveness standard: (1) May 1998 Evidence Guidance[10] and (2) FDAMA 115.[11] Those orphan drugs approved using a single-study approval authority can be found in Tables 2, 3, and 4 highlighted with footnote "a."

May 1998 Evidence Guidance. In May 1998, FDA released its "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (May 1998 Evidence Guidance).[10] This guidance sets out 9 different ways in which a drug may be approved based on a single study; however, in practice, only 1 of these is generally recognized and cited. Too often, in our view, it is this one that is cited by sponsors as a possible basis for approval when it is only applicable in very limited circumstances; that is, this one of the 9 single-study standards from the May 1998 Evidence Guidance applies primarily when there exists a "statistically very persuasive finding [that is] . . . a very low p-value"[10] on the primary endpoint and this is applicable almost always only where to conduct a "second trial would be practically or ethically impossible."[10]

FDAMA 115. At the same time that FDA was working on the May 1998 Evidence Guidance, Congress created an alternative statutory standard for establishing a drug's effectiveness by amending the 1962 effectiveness standard in the Food and Drug Administration Modernization Act (FDAMA) of 1997.[11] Referred to as "FDAMA 115," this new standard allows for approval based on "one adequate and well-controlled clinical study and confirmatory evidence."[11]

The May 1998 Evidence Guidance and FDAMA 115 can be seen as fundamentally similar policies that were fortuitously issued almost simultaneously. One must, however, guard against the conclusion that the May 1998 Evidence Guidance is the sole method for approving a drug based on a single trial. The breadth of the FDAMA 115 "one adequate and well-controlled clinical investigation and confirmatory evidence" statutory standard extends beyond the 9 circumstances described in the May 1998 Evidence Guidance.

Accelerated Approval/Fast Track/Subpart H

The second way in which FDA applies "administrative flexibility" is by relying on an exercise of administration discretion whose source is found in a formal program or policy altering the kind of efficacy endpoint needed for approval (eg, relying on a surrogate endpoint or intermediate clinical endpoint that is "reasonably likely to predict clinical benefit"). Unlike a conventional showing of effectiveness, which relies on a finding on an endpoint measuring clinical benefit (ie, improves how a patient feels, functions, or survives), this type of "administrative flexibility" allows FDA to meet the standard of substantial evidence of effectiveness based on a finding on a surrogate endpoint or intermediate clinical endpoint (ICE).

This system was created by FDA and was in response to the AIDS crisis in the mid-1980s. This FDA system was promulgated as a regulation by FDA under Title 21 of the Code of Federal Regulations Part 314 Subpart H[12] and was therefore informally and often referred to as "Subpart H."

The 1997 FDAMA law created "Fast Track" statutory authority, which was a very modest elaboration by Congress of the earlier FDA-created Subpart H approval pathway, also sometimes referred to as "accelerated approval" (for biologics, the parallel regulation is at Subpart E[12]). Both the Fast Track

Table 1. Substantial Evidence of Effectiveness: "Snapshot" Chart of Authorities and Types of Flexibility.

Conventional Authority and "Single Study" Flexibility		Source of Authority
1	Two adequate and well-controlled studies[a]	21 USC § 355(d)
2	One adequate and well-controlled study with "confirmatory evidence"[b]	21 USC § 355(d) as amended by FDAMA 115
3	One study providing statistically very persuasive evidence and where a second study would be difficult to conduct on practical or ethical grounds[b]	May 1998 Guidance
Types of Flexibility in Addition to "Single Study" Flexibility		
A	Accelerated approval/Subpart H/Fast Track therapies[b]	Historical FDA precedents[d]
B	Case-by-case flexibility for orphan drug therapies[c]	Historical FDA precedents

Source: Modified from the chart proposed in Frank Sasinowski's testimony on May 20, 2014, before the House Energy and Commerce Committee's Subcommittee on Health first hearing of the 21st Century Cures Initiative.[17]
[a]Conventional showing of effectiveness.
[b]Administrative flexibility.
[c]Case-by-case flexibility.
[d]See Sasinowski and Varond.[15]

Table 2. Quantum of Effectiveness Evidence for Orphan Drug Approvals From July 1, 2010, to June 30, 2014: by Chemical Name.

Chemical Name (Brand Name)		Approval (mo/y)	Type of Efficacy Evidence		
			Conventional	Administrative Flexibility	Case-by-Case Flexibility
1	Bedaquiline (Sirturo)[b]	12/2012		✓	
2	Belatacept (Nulojix)	06/2011	✓		
3	Botulism antitoxin hepavalent (BAT)[b]	03/2013		✓	
4	Centruroides scorpion antivenom (Anascorp)[a]	08/2011		✓	
5	Clobazam (Onfi)	10/2011	✓		
6	Coagulation factor XIII concentrate (human) (Corifact)[a,b]	02/2011		✓	
7	Deferiprone (Ferriprox)[b]	10/2011		✓	
8	Droxidopa (Northera)[b]	02/2014		✓	
9	Elosulfase alfa (Vimizim)	02/2014			✓
10	Glucarpidase (Voraxaze)	01/2012			✓
11	Hydroxyprogesterone caproate (Makena)[a,b]	02/2011		✓	
12	Icatibant (Firazyr)[a]	08/2011		✓	
13	Ivacaftor (Kalydeco)	01/2012	✓		
14	Lomitapide (Juxtapid)	12/2012			✓
15	Macitentan (Opsumit)[a]	10/2013		✓	
16	Metreleptin (Myalept)	02/2014			✓
17	Miltefosine (Impavido)[a]	03/2014		✓	
18	Mipomersen (Kynamro)[a]	01/2013		✓	
19	Pasireotide diaspartate (Signifor)	12/2012			✓
20	Pegloticase (Krystexxa)	09/2010	✓		
21	Prothrombin complex concentrate (human) (Kcentra)	04/2013	✓		
22	Raxibacumab (Abthrax)[b]	12/2012		✓	
23	Riociguat (Adempas)	10/2013	✓		
24	Ruxolitinib (Jakafi)	11/2011	✓		
25	Taliglucerase alfa (Elelyso)[a]	05/2012		✓	
26	Tasimelteon (Hetlioz)	01/2014	✓		
27	Teduglutide (rDNA origin) (Gattex)[a]	12/2012		✓	
	Subtotal		8	14	5
	Total		8	19	

[a]Single-study approval authority (May 1998 Evidence Guidance, FDAMA 115).
[b]Accelerated approval/Subpart H/Fast Track.

Table 3. Quantum of Effectiveness Evidence for Orphan Drug Approvals From July 1, 2010, to June 30, 2014: by Brand Name.

	Brand Name (Chemical Name)	Approval (mo/y)	Type of Efficacy Evidence		
			Conventional	Administrative Flexibility	Case-by-Case Flexibility
1	Abthrax (raxibacumab)[b]	12/2012		✓	
2	Adempas (riociguat)	10/2013	✓		
3	Anascorp (centruroides scorpion antivenom)[a]	08/2011		✓	
4	BAT (botulism antitoxin hepavalent)[b]	03/2013		✓	
5	Corifact (coagulation factor XIII concentrate [human])[a,b]	02/2011		✓	
6	Elelyso (taliglucerase alfa)[a]	05/2012		✓	
7	Ferriprox (deferiprone)[b]	10/2011		✓	
8	Firazyr (icatibant)[a]	08/2011		✓	
9	Gattex (teduglutide [rDNA origin])[a]	12/2012		✓	
10	Hetlioz (tasimelteon)	01/2014	✓		
11	Impavido (miltefosine)[a]	03/2014		✓	
12	Jakafi (ruxolitinib)	11/2011	✓		
13	Juxtapid (lomitapide)	12/2012			✓
14	Kalydeco (ivacaftor)	01/2012	✓		
15	Kcentra (prothrombin complex concentrate [human])	04/2013	✓		
16	Krystexxa (pegloticase)	09/2010	✓		
17	Kynamro (mipomersen)[a]	01/2013		✓	
18	Makena (hydroxyprogesterone caproate)[a,b]	02/2011		✓	
19	Myalept (metreleptin)	02/2014			✓
20	Northera (droxidopa)[b]	02/2014		✓	
21	Nulojix (belatacept)	06/2011	✓		
22	Onfi (clobazam)	10/2011	✓		
23	Opsumit (macitentan)[a]	10/2013		✓	
24	Signifor (pasireotide diaspartate)	12/2012			✓
25	Sirturo (bedaquiline)[b]	12/2012		✓	
26	Vimizim (elosulfase alfa)	02/2014			✓
27	Voraxaze (glucarpidase)	01/2012			✓
	Subtotal		8	14	5
	Total		8	19	

[a]Single-study approval authority (May 1998 Evidence Guidance, FDAMA 115).
[b]Accelerated approval/Subpart H/Fast Track.

and Subpart H are programs that authorize FDA to approve a therapy for a serious or life-threatening disease for which there is no FDA-approved "available therapy" based either on an unvalidated surrogate that is reasonably likely to predict a clinical outcome or on an outcome other than irreversible morbidity or mortality that is reasonably likely to predict irreversible morbidity and mortality. For any such approval, there is an additional postapproval requirement to conduct a study to establish the ultimate clinical outcome benefit, and if that study fails to do so, FDA may withdraw its approval on an expedited basis. In addition, a Fast Track designation will provide increased interactions with FDA staff throughout development, and FDA may allow for a rolling review whereby the sponsor may submit portions of a marketing application for review before the sponsor submits the complete application (hereafter, Subpart H and Fast Track will be referred to under the more general umbrella term of "accelerated approval"). Those orphan drugs approved using accelerated approval can be found in Tables 2, 3, and 4 highlighted with footnote "b."

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 formally expanded the scope of the criteria that may qualify a therapy for accelerated approval to specifically consider "those for rare diseases or conditions."[13] While accelerated approval was available to orphan drugs prior to 2012, adding rare diseases to the statutory criteria allows FDA to take the rarity of disease into account in considering whether to consider the accelerated approval pathway.

As follow-up to statutory changes in FDASIA, in May 2014, FDA released its "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics" (May 2014 Expedited Programs Guidance).[14] This guidance lists and describes factors that FDA views as critical to Agency programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the

Table 4. Quantum of Effectiveness Evidence for Orphan Drug Approvals From July 1, 2010, to June 30, 2014: by Date of Approval.

	Brand and Chemical Names	Approval (mo/y)	Type of Efficacy Evidence		
			Conventional	Administrative Flexibility	Case-by-Case Flexibility
1	Krystexxa (pegloticase)	09/2010	✓		
2	Corifact (coagulation factor XIII concentrate [human])[a,b]	02/2011		✓	
3	Makena (hydroxyprogesterone caproate)[a,b]	02/2011		✓	
4	Nulojix (belatacept)	06/2011	✓		
5	Anascorp (centruroides scorpion antivenom)[a]	08/2011		✓	
6	Firazyr (icatibant)[a]	08/2011		✓	
7	Ferriprox (deferiprone)[b]	10/2011		✓	
8	Onfi (clobazam)	10/2011	✓		
9	Jakafi (ruxolitinib)	11/2011	✓		
10	Kalydeco (ivacaftor)	01/2012	✓		
11	Voraxaze (glucarpidase)	01/2012			✓
12	Elelyso (taliglucerase alfa)[a]	05/2012		✓	
13	Abthrax (raxibacumab)[b]	12/2012		✓	
14	Gattex (teduglutide [rDNA origin])[a]	12/2012		✓	
15	Juxtapid (lomitapide)	12/2012			✓
16	Signifor (pasireotide diaspartate)	12/2012			✓
17	Sirturo (bedaquiline)[b]	12/2012		✓	
18	Kynamro (mipomersen)[a]	01/2013		✓	
19	BAT (botulism antitoxin hepavalent)[b]	03/2013		✓	
20	Kcentra (prothrombin complex concentrate [human])	04/2013	✓		
21	Adempas (riociguat)	10/2013	✓		
22	Opsumit (macitentan)[a]	10/2013		✓	
23	Hetlioz (tasimelteon)	01/2014	✓		
24	Myalept (metreleptin)	02/2014			✓
25	Northera (droxidopa)[b]	02/2014		✓	
26	Vimizim (elosulfase alfa)	02/2014			✓
27	Impavido (miltefosine)[a]	03/2014		✓	
	Subtotal		8	14	5
	Total		8	19	

[a]Single-study approval authority (May 1998 Evidence Guidance, FDAMA 115).
[b]Accelerated approval/Subpart H/Fast Track.

treatment of a serious or life-threatening condition, including accelerated approval (and breakthrough therapy).[iii]

The essential aspect of the accelerated approval authority is the concept that a finding on a surrogate endpoint or ICE may be sufficient for meeting the standard of substantial evidence of effectiveness. FDA's May 2014 Expedited Programs Guidance identified the following as the 3 most important factors in FDA's reaching its accelerated approval decisions: (1) understanding of the disease process, (2) understanding of the relationship between the drug's effect on the surrogate or ICE and the disease, and (3) strength of clinical evidence, with strength of clinical evidence broken into 2 subcategories: strength of clinical evidence on the surrogate endpoint or ICE and strength of clinical evidence on the clinical benefit. A recent analysis of FDA precedents by Sasinowski and Varond[15] found that robust compliance with all 3 major factors has not been required by FDA, which is in itself another "type" of exercise of reasonable "flexibility" by the Agency.

Case-by-Case Flexibility

The "case-by-case flexibility" designation is for those orphan drug approvals whose quantum of effectiveness evidence would not either: (1) satisfy the usual and traditional showing of effectiveness (ie, 2 adequate and well-controlled trials) or (2) be considered either a single-study approval (ie, under the May 1998 guidance or FDAMA 115) or an accelerated approval (ie, under Subpart H or Fast Track). Accordingly, this category is one by exclusion.

Dr Janet Woodcock, Director of CDER, and Dr Robert Temple, CDER's Deputy Director for Clinical Science, have responded to criticisms that FDA has not approved many non-cancer, non-HIV therapies using accelerated approval by noting that FDA has given most of the recent new drug approvals for rare diseases traditional approval rather than accelerated approval.[iv] Dr Woodcock, when asked for an example of such a traditional approval where an accelerated approval

may have been considered, cited rare deficiency diseases where drugs provide replacement for the endogenously missing protein or compound. While Dr Woodcock did not identify any specific drug, Aldurazyme (laronidase) for mucopolysaccharidosis I (MPS I) may be one such therapy.[16] However, shifting an accelerated approval to traditional approval would not have altered the findings in Sasinowski[5] or this update in terms of relative percentages of those approvals exhibiting flexibility because that would simply shift that approval between the 2 categories or types of flexibility: from the ''administrative flexibility'' category to the ''case-by-case flexibility'' category.

A Substantial Evidence of Effectiveness "Snapshot" Chart

Another way to organize and display these various ways in which FDA exercises flexibility is shown in Table 1. The ''Snapshot'' chart delineates and organizes, in an uncomplicated and clear way, the 3 existing FDA authorities for the quantum of effectiveness needed, along with the 2 types of demonstrated FDA flexibility in the effectiveness evidence required for approval.[v] Row 1 of the chart corresponds to our ''conventional'' designation. Rows 2, 3, and A of the chart collectively make up our ''administrative flexibility'' category. Finally, Row B of the ''Snapshot'' chart represents our ''case-by-case'' flexibility category (Table 1).

The chart serves as a simple vehicle for FDA to use at Advisory Committee meetings and in the New Drug Application (NDA)/Biologic License Application (BLA) review process.[17] FDA acknowledgement and endorsement of these various existing authorities as well as the types of FDA flexibility would clarify for all stakeholders the full spectrum of available drug therapy approval authorities and FDA's historical flexibility.

Organized together, the first 3 rows of the ''Snapshot'' chart identify the 3 FDA's existing approval authorities (Table 1, Rows 1-3). The final 2 rows of the chart consist of accelerated approval and ''case-by-case flexibility,'' which are the 2 areas in which FDA has been shown, by this analysis and the related analysis of accelerated approval precedents,[15] to have exercised flexibility, historically and consistently, in interpreting the quantum of effectiveness evidence needed (Table 1, Rows A and B).

The ''Snapshot'' chart displays the interplay of these various vital foundations for drug development, review, and marketing approval. In a ''snapshot,'' one can understand, for instance, that while the approval authorities in Rows 1 to 3 are generally alternatives for the quantum of effectiveness evidence required for marketing approval, FDA may still additionally apply either or both of the 2 types of flexibility identified in Rows A and B to any particular therapy under its review.

Results

Tables 2 through 4 present the classification for each of the 27 noncancer orphan therapies approved as new chemical entities for the 4-year period from July 1, 2010, through June 30, 2014. This analysis resulted in classifying 8, or nearly one-third, of the 27 noncancer orphan drugs as having met the ''conventional'' quantum of effectiveness evidence. Of the remaining 19 orphan drug approvals, the analysis classified 14 as ''administrative flexibility'' and 5 as ''case-by-case flexibility.'' Taken together, 19, or just over two-thirds, of the 27 noncancer orphan drugs approved between July 1, 2010, and June 30, 2014, were based on some exercise of flexibility by FDA.

Tables 2 through 4 show the same information organized differently: by chemical name (Table 2), brand name (Table 3), and approval date (Table 4). In Appendix 1, there is a narrative that summarizes the basis for each ''case-by-case flexibility'' classification. In Appendix 2, there is a shorter narrative that identifies the basis for each ''administrative flexibility'' classification.

Discussion

When asked how much evidence of safety and effectiveness an orphan drug must provide, FDA officials still explain that drugs for rare diseases must meet the statutory requirements for safety and effectiveness of any proposed new medicine.[5] While true, this statement without explanation or qualification may be misleading in that it fails to communicate the vital, essential corollary to this, which is: notwithstanding that the statutory standard for therapies for rare diseases is no different than that for all other therapies, FDA has historically and consistently employed considerable, yet reasonable, flexibility in interpreting and applying this statutory standard to therapies for persons suffering with rare diseases.

Since the analysis in Sasinowski,[5] FDA has started to express how it applies flexibility in the orphan drug context. In the May 2014 Expedited Programs Guidance, FDA stated:

> FDA has a history of applying the philosophy underlying subpart E to drugs for rare diseases through use of the Agency's expedited programs. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. FDA will continue to apply flexibility in these situations to address particular challenges posed by each disease.[14] (p. 2)

More recently, on July 11, 2014, before the US House Energy and Commerce Committee's Subcommittee on Health, Dr Woodcock described the impact of FDASIA's Accelerated Approval provisions:

Table 5. Update to Analysis of Orphan Drug Efficacy Evidence.

Orphan Drug Efficacy Evidence	Conventional, n (%)	Total Flexibility, n (%)	Administrative, n	Case-by-Case Flexibility, n
2012 Sasinowski[5] analysis[a]	45 (33.3)	90 (66.7)	32	58
2014 update[b]	8 (29.6)	19 (70.4)	14	5
Total	53 (32.7)	109 (67.3)	46	63

[a]January 1, 1983, to June 30, 2010.
[b]July 1, 2010, to June 30, 2014.

> I think the legislation was very helpful. We have taken it quite seriously. We have issued guidance, final guidance on expedited programs, and probably the biggest change . . . that the legislation brought about was its focus on intermediate clinical end points, and we had to have quite an internal discussion about what that means, and I think you will see us approving more products under accelerated approval based on these intermediate clinical endpoints.[16]

With an increased focus on flexibility, this current analysis classified 14, or 52%, of the 27 noncancer orphan drugs approved by FDA as exercising "administrative flexibility." In other words, more than half of orphan drug approvals were based upon the May 1998 Evidence Guidance, FDAMA 115, and/or Accelerated Approval. Taken together with the 5 orphan drugs approved with evidence that is consistent with a "case-by-case flexibility," 19, or just over two-thirds, of the 27 noncancer orphan drugs approved between July 1, 2010, and June 30, 2014, were based on some exercise of flexibility by FDA. Moreover, this finding is consistent with the proportion of orphan drug approvals in this classification reported in Sasinowski[5] (see Table 5).

This current analysis also revealed 2 instances in which FDA demonstrated 2 different types of flexibility in the same approval, or what we have termed "flexibility squared." Of the 14 orphan drugs that were approved using "administrative flexibility," 12 were based on either one of the single-study approval authorities (eg, May 1998 Evidence Guidance, FDAMA 115) or accelerated approval. As Table 1 illustrates, these approvals received flexibility in meeting the substantial evidence of effectiveness standard or through an alternative approval authority (eg, Accelerated Approval). However, these 2 categories are not mutually exclusive. In 2 instances, FDA approved an orphan product using both types of "administrative flexibility," which we call flexibility squared. Both Corifact and Makena were approved based off just 1 pivotal study of a surrogate endpoint, supporting accelerated approval (see Appendix 2). FDA's use of flexibility squared provides recognition that in certain circumstances, a single pivotal study with a finding on a surrogate endpoint or intermediate clinical endpoint can satisfy the quantum of effectiveness evidence needed for approval. That is, these FDA actions on Corifact and Makena illustrate that FDA may combine 2 (or more) types of flexibility in the same approval decision: in these cases, basing the approval on a single study and on accelerated approval.

Meanwhile, 8, or nearly one-third, of the 27 noncancer orphan drugs in this current analysis were approved using "conventional" quantum of effectiveness evidence, a finding that is consistent with the proportion of orphan drugs in this classification that were approved prior to July 1, 2010 (see Table 5).[5] For these 8 orphan drugs, at least 2 "positive" adequate and well-controlled studies were conducted.

Even in those classified as having met a conventional level of evidence, there may be flexibility as well. For instance, FDA approved one of these orphan drugs with support from 2 adequate and well-controlled studies, but the demonstrated effects were on a surrogate endpoint, and yet this was not an accelerated approval but a traditional approval. When a drug receives a traditional approval, instead of an accelerated approval, the sponsor is not required to conduct a confirmatory trial.[iv]

In each of these classifications, there is an element of subjectivity and judgment. We do not have access to nonpublic information, which both FDA and the sponsors have. It is therefore possible that FDA and drug sponsors will disagree about into which one of these 3 categories any therapy is classified.[vi]

Conclusions

The results of this study show that for just over two-thirds of all noncancer orphan drugs approved between July 1, 2010, and June 30, 2014, FDA did not require the orphan drug applications to provide the conventional level of proof of effectiveness that is ordinarily expected. This is consistent with the results in Sasinowski[5] for orphan drug approvals from January 1, 1983, to June 30, 2010 (see Table 5). Furthermore, in a cumulative analysis of the quantum of effectiveness evidence in FDA's approval of orphan drugs by decade, based on the results of the Sasinowski paper and this study, this level of flexibility has been applied by FDA with remarkable consistency over each of the 3.5 "decades" since the enactment of the Orphan Drug Act in 1983 (see Table 6).

These findings further support Sasinowski's conclusions in 2012 that FDA has demonstrated extraordinarily reasonable flexibility in its review of certain applications for orphan drugs.

Table 6. Analysis of Orphan Drug Efficacy Evidence by Decade.

Orphan Drug Efficacy Evidence Time Period	Conventional, n (%)	Total Flexibility, n (%)	Administrative, n	Case-by-Case Flexibility, n
1983[a] to 1989	7 (33.3)	14 (66.7)	5	9
1990 to 1999	21 (35.6)	38 (64.4)	13	25
2000 to 2009	13 (26.5)	36 (73.5)	13	23
2010 to 2014[b]	12 (36.4)	21 (63.6)	15	6
Total	53 (32.7)	109 (67.3)	46	63

[a]Beginning in January 1983, the date of enactment of the Orphan Drug Act.
[b]Through June 30, 2014.

These findings also further reinforce the need for FDA and sponsors to better understand and discuss the various types of administrative flexibility. As previously described, Table 1 illustrates the options for meeting the substantial evidence of effectiveness standard, including through 2 alternative single-study approval authorities, through expedited programs (eg, Accelerated Approval), and through the type of case-by-case flexibility that FDA has historically applied to orphan drugs. The chart is an uncomplicated and clear way to present and make available for consideration these various pathways for demonstrating efficacy. Utilization of such a tool, based on over 3 decades of FDA precedents, would focus FDA and sponsors on considering the appropriateness of FDAMA 115, the May 1998 Guidance, Accelerated Approval pathway, as well as other unique considerations of orphan drug development throughout the entire development process, especially from the pre–Investigational New Drug (IND) meeting through the review of, and action on, the marketing application.

It has now been over 30 years since the Orphan Drug Act was enacted and provided incentives for developing orphan drugs, yet the vast majority of the estimated 30 million Americans suffering with rare diseases do not yet have a single FDA-approved therapy. These patients and their families have a vital and urgent need for faster development of therapies and are relying on industry, FDA reviewers, and other stakeholders to make maximum use of all facets of the system for orphan drug development. This study reinforces that the FDA component of this system has a proven vast capacity for exercising reasonable flexibility in advancing the availability of new therapies for those with this great unmet medical need.

Appendix 1: Case-by-Case Flexibility

This appendix provides commentary on the basis for approval for those therapies whose approval was categorized as "case-by-case flexibility." The appendix is keyed to the product numbering system in Table 2, and as such, it starts with the ninth drug listed in Table 2 because it is the first in the "case-by-case flexibility" classification.

9. Elosulfase alfa (Vimizim)

This February 2014 approval of this first therapy for treating patients with mucopolysaccharidosis (MPS) IVA or morquio A syndrome was established on the basis of a single, randomized 24-week placebo-controlled trial of 176 patients with MPS IVA. Patients were randomized 1:1:1 to Vimizim 2 mg/kg every other week (QOW), every week (QW), or placebo. The primary endpoint was change from baseline in the distance walked in 6 minutes (6MWD) at week 24, with 2 prespecified secondary endpoints of (1) change from baseline to week 24 in the number of stairs climbed in a 3-minute stair climb (3MSC) and (2) change from baseline to week 24 in urine keratan sulfate (uKS) levels. In her memo accompanying this approval, the deputy office director explained the various efficacy results in this single study this way: Patients in the Vimizim 2 mg/kg QW treatment group demonstrated a statistically significant mean change in the 6MWD of 22.5 meters ($P = .0174$) relative to placebo. The mean difference between the QOW group and the placebo group was 0.5 meters and was not statistically significant ($P = .9542$). Patients in the QW treatment group demonstrated a mean change of 1.1 stairs/minute ($P = .4935$) relative to placebo; patients in the QOW treatment group demonstrated a mean change of –0.5 stairs/minute ($P = .7783$) relative to placebo (that is, numerically worse than placebo). Both the QW and QOW treatment groups demonstrated a statistically significant reduction in the uKS levels relative to placebo, 30.2% ($P < .0001$) and 40.7% ($P < .0001$) for the QOW and QW treatment groups, respectively. The relationship between uKS levels and other measures of clinical response has not been established.[18]

In explaining her decision to approve this therapy, the deputy office director stated that the heterogeneity of the disease in terms of its presentation and progression makes it difficult to rely on a single endpoint that has clinical meaningfulness for all MPS IVA patients. The 6MWT, which measures the

integrated function of at least 3 separate organ systems that are affected by MPS IVA, the respiratory, cardiovascular, and musculoskeletal systems, was agreed to by FDA as an appropriate primary endpoint for the pivotal phase 3 trial. At the November 19, 2013, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), the majority of committee members agreed that the 6MWT is adequate to evaluate the treatment benefit in patients with MPS IVA, although they acknowledged that the test does not fully evaluate treatment benefit and does not include some of the important aspects of the disease manifestations, such as pain and fatigue. The pivotal trial (MOR-004) demonstrated a statistically significant mean change in the 6MWD of 22.5 meters ($P = .0174$) relative to placebo; however, the review team questioned the clinical meaningfulness of this modest treatment effect. EMDAC members opined that the totality of the data (including whether the magnitude of treatment difference observed in the 6MWT represented a clinically meaningful benefit) supported the effectiveness of Vimizim. The treatment effect of Vimizim is further bolstered by the subset of Vimizim-treated patients who achieved an improvement in 6MWD of $\geq$100 meters change from baseline to Week 24. And while the extension trial data demonstrated no further improvement in the 6MWD with continued therapy to 72 weeks, it is reassuring that it did demonstrate stabilization in walking ability over time.[18]

In sum, FDA approved Vimizim on a single trial in which only 1 of 2 investigational dose arms was positive on the primary endpoint and where the FDA characterized the magnitude of this positive result as "modest" and where FDA questioned the clinical meaningfulness of this result. In addition, the only other prespecified secondary endpoint that measured a clinical outcome, 3MSC, did not approach statistical significance in either of the 2 investigational dose arms.

Given this design and the results, FDA likely would not have viewed it as unethical to conduct a second trial, and the magnitude of the results on the 6MWD endpoint would likely not be viewed by FDA as "statically very persuasive"; therefore, this approval is not likely to be one in which FDA would have applied its May 1998 single-study approval standard.[11]

Accelerated approval based on the statistically highly persuasive uKS surrogate findings would not likely have been an option given that FDA had noted that the "relationship between uKS levels and other measures of clinical response has not been established." FDA may have considered accelerated approval based on the intermediate clinical endpoint (ICE), the 6MWD results.

The third type of FDA "administrative flexibility" is under the "single adequate and well-controlled clinical trial plus confirmatory evidence" standard created by FDAMA 115; however, this would not seem to be applicable here either given that there were not other clinical trials, nor other closely related pharmacological therapies that had been approved for this condition.

Consequently, we in this article have classified Vimizim under "case-by-case flexibility."[19]

10. Glucarpidase (Voraxaze)

In this January 2012 approval of this therapy for treating cancer patients with "toxic plasma methotrexate concentrations (>1 μmol/L) in patients with delayed methotrexate clearance due to impaired renal function," the FDA and the sponsor chose to assess the effectiveness of this therapy in a subset of 22 subjects in 1 of 2 trials that FDA determined to be "major trials supporting efficacy and safety in [this] application," which enrolled a total of over 400 subjects.[20] In addition there were 3 additional "legacy" trials that enrolled almost 400 subjects that used another lot of the investigational drug.[20] Further, with respect to these 22 subjects, FDA recognized that "it was known at the time the SAP was submitted that there were 27 subjects with these samples submitted" (that is, that met the per protocol evaluable definition of the substudy population). Of these 27 subjects, 22 were eligible and evaluable.[20]

The following is from the FDA Medical Review for this therapy:

> The clinical recommendation for this biologic license application (BLA) 125357 for Voraxaze (glucarpidase) is approval. The indication is for the treatment of toxic plasma methotrexate (MTX) concentrations due to impaired renal function. Controlled trials for this indication were not feasible. The evaluation of efficacy was based on a pharmacodynamic endpoint.
>
> The pharmacodynamic efficacy endpoint supporting this application is the proportion of subjects with an elevated methotrexate level prior to glucarpidase administration who demonstrate a rapid and sustained methotrexate level $\leq$1 μmol/L after glucarpidase therapy. The analysis of this endpoint was carried out in a subset of patients entered on a National Cancer Institute–sponsored study with central laboratory high-performance liquid chromatography (HPLC) measurement of post glucarpidase plasma methotrexate concentration. Glucarpidase was administered at a dose of 50 units/kg. There were 22 patients eligible for the efficacy analysis. Ten patients achieved a response (45.5% [95% CI, 26.9%-65.3%]) after a single dose of glucarpidase. The percentage reduction of methotrexate concentration was an exploratory endpoint. In 20 of 22 patients, the methotrexate concentration was reduced and maintained greater than 95% from baseline preglucarpidase level up to 8 days.
>
> Of note, glucarpidase therapy failed to prevent fatal methotrexate toxicity in 3% of patients. Among the 290 patients included in the safety population who received glucarpidase, there were 8 deaths consistent with the sequelae of methotrexate toxicity within 30 days of glucarpidase exposure not related to progressive disease.

> The safety evaluation of glucarpidase was complicated because it was not feasible to conduct controlled trials for this indication. The population suffers from extensive baseline toxicity. Patents with delayed methotrexate clearance develop life-threatening complications including hematopoietic suppression, renal dysfunction/failure, hepatic dysfunction/failure, mucositis, and infections.
>
> In the safety population, the most common adverse events related to glucarpidase administration were parasthesia, flushing, nausea and/or vomiting, hypotension, and headache. All adverse reactions were grade 1 or 2, except for 1 episode of flushing categorized as grade 3.[20] (p. 9)

With respect to the deaths described previously, there are 2 aspects of this to note: First, the failure rate that resulted in deaths was reported as 3% from the 2 trials from which the 27 subjects were selected as the sole primary evidence of effectiveness; however, "this failure rate was greater (25/327, 8%) in the trials using the [earlier lot, that is, the 'legacy' trials]"[20]; and second, there was no report on the historic or natural history rate of death in similar subjects who were not on the investigational drug, that is, no comparator rate against which to assess this reported failure rate that led to 3% to 8% of deaths not due to cancer disease progression but due to events "consistent with the sequelae of methotrexate toxicity."

Finally, it may also be noteworthy that there is no report on what happened to the overwhelming majority of subjects who enrolled in the 2 major studies that did not meet the criteria for evaluation; that is, the approximately 400 subjects who were enrolled in these 2 studies but were not selected for efficacy assessment. Usually such analyses of methotrexate levels immediately after intervention (the primary pharmacodynamic endpoint of methotrexate levels 15 minutes after drug administered and 8 days later) would be presented even if just as sensitivity analyses.

The absence of a single "adequate and well-controlled trial," due to feasibility issues, means on its face that this approval fails to satisfy either the "conventional" standard for approval or one of the "administrative flexibility" single-study approval authorities. Additionally, FDA did not consider the prespecified analysis of the pharmacodynamic efficacy endpoint in a subgroup of subjects, a finding on a surrogate endpoint, or ICE to support accelerated approval. Consequently, in this study we have classified Voraxaze under "case-by-case flexibility."

14. Lomitapide (Juxtapid)

FDA in its December 2012 approval of this therapy "to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo-B), and non–high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesteremia (HoFH)" based its efficacy determination on the results of 29 patients after 26 weeks of therapy in a single-arm, open-label trial.

The primary efficacy endpoint in both trials (the second study was a phase 2 study with 6 subjects that FDA concluded provided "supportive evidence") was the percentage change from baseline to endpoint in directly measured serum LDL-C; each subject served as his or her own control. The surrogate endpoint of serum LDL-C has been an accepted primary efficacy measure in marketing applications for lipid-lowering therapies in the US. The relationship between reductions in LDL-C levels and decreased risk of adverse cardiovascular outcomes has been well established for statin therapy. Although there are no data correlating LDL-C reduction and improved cardiovascular outcomes for (this pharmacological class of therapies), there is no reason to believe that LDL-C would not be an acceptable efficacy endpoint for HoFH patients treated with lomitapide. Moreover, a definitive cardiovascular outcomes trial in HoFH patients would be infeasible because of the rarity of the disease, and LDL-C is the most appropriate surrogate measure available.[21]

"At week 26, the mean and median percent changes in LDL-C from baseline were –40% (paired t-test $p < 0.001$) and –50%, respectively."[22] "Drug benefit was also observed for other lipid parameters, such as total cholesterol, apo B, and non-HDL-C."[21] In addition, FDA cited the "supportive data from the HoFH-pilot study [whose] findings demonstrate a dose response indicating a drug effect of lomitapide."[22]

A lone single-arm, open-label study with supportive data from a phase 2 pilot study does not constitute even a single "adequate and well-controlled study" to satisfy either the "conventional" standard for approval or 1 of the "administrative flexibility" single-study approval authorities. As discussed in the FDA review, LDL-C would likely have been a clinical endpoint that could be the basis for a traditional approval and was not deemed by FDA to be a finding on a surrogate endpoint or ICE to support accelerated approval. Consequently, we have here classified Juxtapid under "case-by-case flexibility."

16. Metreleptin (Myalept)

In its February 2014 approval of this therapy "to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy," FDA relied on 12-month results pooled from 2 open-label, investigator-sponsored single-arm trials of 48 subjects with generalized lipodystrophy conducted at the NIH. In the medical officer's "efficacy summary," she begins by stating:

> Without a placebo group or adequate historical control, it is challenging to attribute beneficial changes to metreleptin versus improvements in diet or enhanced compliance with concomitant antihyperglycemic or lipid-lowering medications.

> Furthermore, a substantial amount of missing data, variable duration of therapy, variation in the timing of efficacy assessments, variable and within-trial adjustment of background therapies, compliance that was not systematically documented, and protocol changes add to the challenges of isolating the effect of metreleptin on metabolic control in this application.[23]

Elsewhere in her review, she raises a hypothetical question to highlight the nature of confounding factors in this trial. With respect to the key endpoints of hemoglobin A1C (A1C), fasting plasma glucose (FPG), and fasting triglycerides (fasting TG), the reviewer asks: "For example, should a patient be considered a 12-month 'responder' for improvement in triglycerides if she was newly started on fenofibrate prior to the 12 month visit?"[23] In her review, the deputy office director cites an example that Dr Golden presented in her Advisory Committee presentation: With respect to NIH Patient 90162, Dr Golden pointed out that there was a notable 2.2% reduction in A1C by Month 12.[24] However, Dr Golden was able to identify the initiation of metformin 500 mg bid at Month 8 in this patient. The observed improved glycemic control could have been due in part to this metformin therapy and raises doubts whether all improvement observed was due to metreleptin alone.[23] Other examples of concomitant medication use confounding data interpretation are presented in Dr Golden's review, underscoring the difficulty in evaluating the true effect of metreleptin in many of these cases. The medical officer further notes that "all efficacy analyses are considered to be post-hoc."[23]

The deputy office director summarized the FDA conclusions this way: "Despite the study design challenges, I believe there was sufficient evidence that metreleptin contributed significantly to the improvements of glycemic parameters and hypertriglyceridemia .... Although use of concomitant therapies clouded the assessment of efficacy ..., there were notable examples of patients with generalized [lipodystrophy] who had significant reductions in HbA1c and discontinuation of their anti-diabetic therapies, lending support to a conclusion that metreleptin favorably impacted insulin resistance in these patients."[24] (pp. 18-19)

Here, FDA's approval decision did not seem to rely on even a single "adequate and well-controlled study" that would have satisfied either the "conventional" standard for approval or one of the "administrative flexibility" single-study approval authorities. Instead, the quantum of effectiveness evidence consisted of notable individual (sometimes referred to as "anecdotal") cases of significant clinical improvement. As such, there was no finding on a surrogate endpoint or ICE to support accelerated approval. Consequently, we have here classified Myalept under "case-by-case flexibility."

19. Pasireotide Diaspartate (Signifor)

In the December 2012 approval of the drug for treatment of adult patients with Cushing disease (CD), efficacy was demonstrated in a 6-month study in 162 subjects with CD (Trial 2305). The trial had a small sample size and did not include an active control or placebo comparator arm because it was deemed to be unethical in this patient population.

"The primary efficacy endpoint was a stringent one, with a response defined by normalization of [mean urinary free cortisol (mUFC)] without a dose increase needed to achieve that at Month 6. The prespecified primary efficacy analysis stipulated that response rates be estimated within individual treatment groups and each rate compared with a pre-specified noninferiority margin of 15%. The 900 μg dose (given twice daily) met the primary efficacy criterion."[25] (p. 30) "Although the 600 μg dose did not meet the primary efficacy criterion, one can not declare that the two doses are different statistically. This is because Study 2305 was not powered to differentiate between doses and there was no plan to formally test for statistical differences in mUFC between dose groups."[25] (p. 31)

The division director stated "the criterion for declaring a statistically significant treatment effect was an arbitrarily set one and the absence of a placebo arm precludes [FDA] from declaring that the effect observed with the 600 μg bid dose was also significant. In addition, the trial was not powered to demonstrate a difference in effect between the two doses. And finally, while the trial randomized patients to the two different doses, a numeric imbalance in the baseline UFC might also contribute to the lower rate of UFC normalization in the 600 μg bid group."[26] (p. 6)

There was a baseline imbalance favoring the high-dose group due to its lower mUFC baseline level, so it was easier for the high-dose group to get to the primary endpoint of normalization of mUFC levels. However, when the definition of responder was changed to "a patient with mUFC $\leq$ ULN or 50% reduction from baseline," there was almost no difference between the 2 groups (34% vs 41%), and this too would have been affected by the baseline imbalance and may be the real reason for even this small numerical advantage for the higher dose group.

Pasireotide has demonstrated efficacy in decreasing UFC as a measure of treatment of CD. However, pasireotide also was associated with the development of glucose intolerance/diabetes/worsening diabetes control in patients. The reason for this, as described by the sponsor, is that SSTR5 receptor stimulation leads to decreased insulin secretion. There is evidence in the data that other clinical manifestations of CD improved in some, but not all patients, including blood pressure control and fat redistribution. Therefore, a paradox exists whereby pasireotide decreases urinary cortisol, a good

marker for decreased ACTH secretion, but has an adverse effect on glucose homeostasis, which is also one of the main consequences of CD and where corrective therapy would be welcomed. This was a focus of discussion at the November 7, 2012, Advisory Committee meeting where the general consensus was that use of pasireotide, while possibly worsening glucose control, did have enough evidence of other benefits to allow marketing.[27]

The approval decision reflects that in a single study without a placebo or another control, other than slightly different comparator dose arms, the primary efficacy endpoint was not met and had mixed, including negative, effects on other clinical manifestations of the condition. There was no placebo control arm due to ethical concerns, so on its face this approval fails to satisfy either the "conventional" standard for approval or one of the "administrative flexibility" single-study approval authorities. Additionally, FDA did not consider the combination of other benefits a finding on a surrogate endpoint or ICE to support accelerated approval. Consequently, we have here classified Signifor under "case-by-case flexibility."

Appendix 2: Administrative Flexibility

This appendix provides brief commentary that identifies the basis for approval for those therapies whose approval was categorized as "administrative flexibility." The appendix is keyed to the product numbering system in Table 2, and as such, this appendix starts with the first drug listed in Table 2 because it is the first in the "administrative flexibility" classification.

1. Bedaquiline (Sirturo)

In its December 2012 approval of the drug for treatment of patients with multi–drug-resistant tuberculosis, FDA approved the drug under Subpart H.[12] In the 2 studies supporting accelerated approval, the surrogate endpoint for successful treatment of tuberculosis was time to sputum culture conversion to negative, which was defined as the interval in days between the first dose of study drug and the date of the first of 2 consecutive negative sputum cultures collected at least 25 days apart during treatment.[28]

3. Botulism Antitoxin Hepavalent (BAT)

FDA's March 2013 approval of the drug for treatment of symptomatic botulism poisoning was based on efficacy studies conducted in animal models of botulism pursuant to the Animal Efficacy Rule.[29,30] Human subjects studied in clinical trials were normal volunteers, none of whom were symptomatic or had been exposed to toxin before administration of the test product, not allowing generalization to the target patient population, which led to the animal rule decision.[31]

4. Centruroides Scorpion Antivenom (Anascorp)

In the August 2011 approval of the drug for treatment of patients with clinical signs of scorpion envenomation, efficacy was demonstrated under either or both of the single-study approval authorities (ie, May 1998 Evidence Guidance, FDAMA 115). Evidence of efficacy was generated from just 1 prospective double-blind, randomized, placebo-controlled study (consisting of 13 patients with scorpion envenomation) with additional, possibly confirmatory evidence from 4 open-label studies and 1 retrospective study.[33] Combined, the studies included a total of 1534 patients, and 95% to 100% were relieved of systemic signs associated with scorpion envenomation in less than 4 hours after initiating Anascorp[32] treatment, whereas in the historical control database, only 3.1% of patients experienced relief of symptoms within 4 hours of hospital admission.[33,vii]

6. Coagulation Factor XIII Concentrate (Human) (Corifact)

In its February 2011 licensure of the drug for routine prophylactic treatment of congenital Factor XIII deficiency, FDA approved the drug under Subpart H[viii] using a single-study approval authority (ie, May 1998 Evidence Guidance, FDAMA 115).[34] In the 1 pivotal pharmacokinetics study supporting accelerated approval, the surrogate endpoint was based on maintaining a trough factor XIII activity level of approximately 5% to 20%.[34] A total of 12 clinical trials were included in the BLA application with a total of 3590 doses of Factor XIII concentrate (human) administrated to subjects with the deficiency.[34]

7. Deferiprone (Ferriprox)

In its October 2011 approval of the drug for treatment of patients with transfusional iron overload due to thalassemia syndromes, FDA approved the drug under Subpart H. Approval was based on a 236-patient prospective, planned, pooled analysis of patients from several studies, using a historical control, which FDA determined had the necessary characteristics of an adequate and well-controlled study.[35,ix] In this "single study" supporting accelerated approval, the surrogate endpoint was reduction in serum ferritin.[35]

8. Droxidopa (Northera)

In its February 2014 approval of the drug for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension, FDA approved the drug under Subpart H.[36] In the 3 well-controlled studies that "collectively support efficacy" for this accelerated approval, the intermediate clinical endpoint (ICE) was itself a bit unusual in that the efficacy finding was on dizziness, the clinical manifestation that is the "hallmark" of this disease, but the finding of effectiveness on reducing dizziness was only at 1 week, a very short-term effect for a chronic condition.[36] In this case, FDA concluded that the short-term effect on dizziness was reasonably likely to predict the long-term, or chronic, effect on this same endpoint, dizziness, in this chronic condition.[36,37]

11. Hydroxyprogesterone Caproate (Makena)

In its February 2011 approval of the drug to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth, FDA approved the drug under Subpart H using a single-study approval authority (ie, May 1998 Evidence Guidance, FDAMA 115). In the 1 adequate and well-controlled trial, reduction in the proportion of women who delivered preterm at less than 37 weeks ($P = .0003$) was found to be an adequate unvalidated surrogate endpoint for reduction in neonatal morbidity and mortality.[38]

12. Icatibant (Firazyr)

In the August 2011 approval of the drug for treatment of acute attacks of hereditary angioedema, substantial evidence of effectiveness was demonstrated under FDAMA 115. Effectiveness was demonstrated in 1 adequate and well-controlled study with robust results and confirmatory evidence consisting of 2 adequate and well-controlled studies that FDA considered confirmatory.[39] FDA found that the other 2 studies were not sufficient to meet the standard of substantial evidence of efficacy for approval because: (1) The placebo-controlled study did not demonstrate efficacy but trended in the correct direction, and (2) the active-controlled study, with tranexamic acid as the active control, demonstrated a statistical finding that conventionally would constitute adequate evidence of effectiveness, but this study had several design elements that made interpretation difficult.[39]

15. Macitentan (Opsumit)

In the October 2013 approval of the drug for the treatment of pulmonary arterial hypertension (PAH) to delay disease progression, efficacy was demonstrated under the May 1998 Evidence Guidance single-study approval authority. Evidence of efficacy was generated from just 1 adequate and well-controlled trial, with the primary endpoint defined as time to death, the first significant morbidity, or clinical worsening of PAH ($P < .0001$).[40,41]

17. Miltefosine (Impavido)

In the March 2014 approval of the drug for 3 indications (visceral leishmaniasis [VL], cutaneous leishmaniasis [CL], and mucosal leishmaniasis [ML]), for each indication, efficacy was demonstrated under either or both of the single-study approval authorities (ie, May 1998 Evidence Guidance, FDAMA 115).[42] For VL, 1 randomized, open-label study conducted in India in 1999-2000 demonstrated that miltefosine was noninferior to amphotericin B and was supported by a randomized, open-label trial conducted in Ethiopia in 2003-2005.[42] For CL, 1 randomized trial conducted in Colombia and Guatemala in 2000-2002 demonstrated the superiority of miltefosine over placebo and was supported by an open-label study conducted in Bolivia in 2005-2007 and a randomized, open-label trial conducted in Brazil in 2007-2009.[42] For ML, 1 single-arm, historically controlled study conducted at a single site in Bolivia in 2004-2006 was persuasive when supported by the studies for VL and ML.[42] The May 1998 Evidence Guidance provides a single-study approval authority where the study is of a "new use, with independent substantiation from related study data."[10] Specifically, the guidance provides for this authority when the studies are in a closely related disease, meaning in "etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases."[10] Therefore, FDA may have relied on the single studies in each disease, even though 1 of 3 studies was uncontrolled, to support approval for the other closely related leishmaniasis diseases.

18. Mipomersen (Kynamro)

In the January 2013 approval of the drug for treatment of homozygous familial hypercholesterolemia (HoFH), efficacy appears to have been demonstrated under the FDAMA 115 single-study approval authority. Evidence of efficacy was generated from just 1 adequate and well-controlled trial in HoFH patients ($P < .001$) with supportive evidence from 3 clinical trials in non-HoFH patients with dyslipidemia.[43,44] All 4 trials were identical in design: multicenter, randomized, double-blind, placebo-controlled, parallel arm with a 2:1 randomization to mipomersen or placebo with a primary efficacy endpoint of change in percentage of serum LDL-C (a surrogate endpoint that has been accepted by FDA as a primary efficacy measure for traditional approval for lipid-lowering therapies).[43]

22. Raxibacumab (Abthrax)

FDA's December 2012 approval of the drug for treatment of inhalational anthrax was based on efficacy studies conducted in animal models of inhalational anthrax pursuant to the Animal Efficacy Rule.[29,45] Inhalational anthrax is a disease for which it is not ethical or feasible to conduct a controlled clinical trial.[46]

25. Taliglucerase Alfa (Elelyso)

In the May 2012 approval of the drug for long-term enzyme replacement therapy (ERT) for adults with type 1 Gaucher disease, efficacy was demonstrated under either or both of the single-study approval authorities (eg, May 1998 Evidence Guidance, FDAMA 115). Evidence of efficacy was generated from just 1 randomized, double-blind, controlled trial in treatment-naïve patients ($P < .0001$ for both the 30 units/kg and 60 units/kg arms),[47,48] with support from an open-label study in patients who had been receiving treatment with imiglucerase as well as from an extension study.[49,50]

27. Teduglutide (rDNA origin) (Gattex)

In the December 2012 approval of the drug for treatment of adult patients with short bowel syndrome who are dependent on parenteral support, efficacy was demonstrated under the FDAMA 115 single-study approval authority in that its evidence of efficacy was generated from just 1 adequate and well-controlled trial ($P = .002$), with support from a clinical trial that did not meet the primary endpoint but showed a numerical advantage over placebo.[51-53]

Notes

[i]Sasinowski[5] has been widely cited, such as in the September 2012 President's Council of Advisors on Science and Technology (PCAST) report, "Propelling Innovation in Drug Discovery, Development, and Evaluation"[54] and many times in FDA publications and presentations, including FDA's July 2014 pediatric rare diseases report and strategic plan.[55]

[ii]Many other Center for Biologics Evaluation and Research (CBER) BLAs were listed as new biologics but were excluded from this analysis because we did not consider them equivalent to a new chemical entity. For example, Alprolix (coagulation factor IX α-subunit [recombinant]) and Rixubis (coagulation factor IX [recombinant]) were listed as new biologics, but we did not include them because other coagulation factor IX BLAs were previously approved.

[iii]FDASIA14 Section 902 provided for a new "Breakthrough Therapy" designation that is granted to a drug intended to treat a serious or life-threatening disease and has preliminary clinical evidence of substantial improvement in treatment on clinically significant endpoints. While none of the orphan drugs that were approved up to June 30, 2014, received a Breakthrough Therapy designation, it is worth noting that it is another mechanism for "administrative flexibility." A feature of the Breakthrough Therapy designation is a compressed drug development program, where alternative clinical trial designs are considered, which FDA notes "may be especially useful in studies in rare diseases."

[iv]See, for example, Woodcock J. FDA's final guidance on expedited drug approvals: fueling innovation and helping patients.[56]

[v]The "Snapshot" chart was adapted from the chart proposed in Frank Sasinowski's May 20, 2014, testimony at the inaugural hearing on the 21st Century Cures Initiative before the House Energy and Commerce Committee's Subcommittee on Health.[17]

[vi]A further cautionary note is that every drug approval, whether for a rare condition or a common one, stands on a unique set of empirical evidence judged against a backdrop of specific scientific and clinical considerations in light of the relative degree of the medical needs of that particular set of patients. Therefore, caution must be exercised in any attempt to extrapolate from any one or more of these case studies to current or future therapies in development or under FDA review.

[vii]In addition to this approval possibly being based on either or both of the single-study approval authorities, it may too be another example in which FDA "flexibility" considered natural history comparator under 21 CFR 314.126(b)(2)(v).

[viii]The equivalent provision to 21 CFR 314 Subpart H for biologics is 21 CFR 601 Subpart E.[12]

[ix]In addition to this approval possibly being based on Subpart H, it may too be another example of where FDA "flexibility" considered natural history comparator under 21 CFR 314.126(b)(2)(v).

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