The Journal of Rare DISORDERS

WHY DOES USE OF EXPEDITED APPROVAL METHODS VARY SO GREATLY? AN ANALYSIS OF ORPHAN DRUGS APPROVED IN 2014

John Ansell, MA, and Glenn Tillotson, PhD

TranScrip Partners, Reading, United Kingdom

ABSTRACT

The US Food and Drug Administration (FDA) now provides 4 different methods for expediting approval of new drugs. This article examines how companies employed these options to win FDA approval last year for 17 orphan drugs and examines the diverse issues encountered.

For the first time, in 2014, the Priority Review option was used by all companies whose orphan drugs were successfully registered. This represented a sharp increase in its usage, given that just under half of all companies gaining approval for orphan products had used this option in both 2012 and 2013. In contrast, since 2013 there has been little change in the extent to which the other 3 methods for expedited approval have been used for orphan products.

Other than the universal use of the Priority Review option, we find remarkable variation in the options taken for expedited approval for orphan drugs in 2014: no less than 7 different combinations of the 4 methods were taken. Consequently, we believe this indicates that the options are neither fully understood by orphan drug companies or are not being used optimally by them—with this marked variation relating less to a correct analysis of likelihood of qualification than to companies' internal attitudes toward the ease of proceeding via each method. It is also unclear why companies do not avail themselves more of the four options. Limited resources or inexperience with the different methods could well be playing a role.

We suggest that there is now a case for granting automatic Priority Review status for all drugs granted orphan status and the scope for rationalizing, unifying, and thereby simplifying the 4 methods. This would benefit developers of all types of drugs, but particularly of orphans, as well as reduce the impact of increasing usage of FDA resources.

INTRODUCTION

Orphan drug status applies to drugs that are developed for a specific condition or disease (there are more than 7000 recognized rare diseases) affecting fewer than 200,000 Americans. In the United States, the Office of Orphan Products Development administers the major provisions of the Orphan Drug Act, which provide incentives for sponsors to develop products for rare diseases. The Orphan Drug Act has been very successful—more than 400 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than 10 such products reach the market.[1]

This regulatory status has several benefits for the sponsor, including marketing the drug without competition for 7 years and possible qualification for clinical trial tax incentives. Awareness of orphan conditions has increased significantly over the past decade for a number of reasons, not least of which is the response by the US Food and Drug Administration (FDA) to enhancing or simplifying the process for approval.

The European Union (EU) has enacted similar legislation, Regulation (EC) No 141/2000, in which pharmaceuticals developed to treat rare diseases are referred to as "orphan medicinal products." The EU's definition of an orphan condition is broader than that of the FDA's, in that it also covers some tropical diseases that are primarily found in developing nations. In Europe the medicine must treat, prevent, or diagnose a life-threatening or chronically debilitating condition, and this condition must affect fewer than 5 in 10,000 people in the EU. Alternatively, if a condition affects more than 5 in 10,000 people in the EU, it may still be considered for orphan designation. Notably, for a treatment to qualify for orphan designation, there must be no existing approved treatments for the indicated condition, or if there are, the product in question must offer significant improvements over the other options. Orphan drug

Orphan drug status granted by the European Commission gives marketing exclusivity in the EU for 10 years after approval. The EU's legislation is administered by the Committee on Orphan Medicinal Products of the European Medicines Agency. In 2014, seventeen orphan drugs were approved for clinical use in Europe, a remarkable increase compared with previous periods.[2]

THE 4 METHODS FOR EXPEDITED APPROVAL IN THE UNITED STATES

Orphan drug status, in itself, provides various benefits to drug development companies that include measures to expedite approval. But, in addition, as for all drugs, orphans can qualify for any of the FDA's 4 methods of expedited approval. This article examines how companies with orphan drugs approved in 2014 are availing themselves of these options.

The box shows the 4 different methods of expedited approval available to drug developers. The methods have much in common; in particular, all 4 methods target therapies intended to treat a serious aspect of a condition or a serious condition. Also, all require that a new compound address an unmet medical need.[3]

ANALYSIS OF EXPEDITED APPROVAL METHODS FOR ORPHAN DRUGS APPROVED IN 2014

In 2014 the FDA approved 41 new drug applications, of which 17 were orphans, all from different companies.[4] Details are shown in the **table**. The 17 orphan drugs dominated successful usage of the 4 different methods for expedited approval that have evolved:

Priority Review:
Just over two-thirds (17/25) of all Priority Review approvals were orphans.

Fast Track:
Just over half (10/17) of all Fast Track approvals were of orphan drugs.

Accelerated Approval:
All 8 of the Accelerated approvals were orphans.

Breakthrough Therapy:
Over two-thirds (7/9) of all Breakthrough approvals were orphans.

Variety of Options Taken for Orphan Products

All 17 orphan drugs approved in 2014 had been granted Priority Review status (compared with only a third of non-orphan products that were granted this status). This is a recent development: in both 2012 and 2013, just under half of all orphan drugs approved (6/13 and 4/9, respectively) were granted this status.

There was also considerable, though lesser, use of the other 3 options for orphan drugs, as shown in **Figure 1**: 10 received Fast Track status, 8 had Accelerated status, and 7 were designated as Breakthrough. For each of these methods, the proportions of orphan drugs approved in 2014 were similar to those in the 2013 cohort.

The extent to which companies used different options varied enormously. **Figure 2** depicts the distribution of use for each of the 4 methods. Only 2 companies used all 4 methods, 7 used 3 methods, and 5 used 2 methods. Three companies used just 1 method.

Underlining the degree of variety of approaches used was the remarkable diversity in combinations of methods used. These are shown in **Figure 3**.

As mentioned previously, all 4 options were used by just 2 of the companies whose orphan drugs, Opdivo (nivolumab) and Zydelig (idelalisib), were approved in 2014.

As Figure 3 shows, no less than 7 combinations of the 4 possible expedited approval methods were used. All 3 possible combinations of the 4 options were used, and 2 types of combinations of just 2 of them. However, the only method used alone was Priority Review. Thus, there was a very wide variety of patterns of usage of the 4 methods. Although the most popular of the 7 different combinations was Priority + Accelerated reviews, this was still only used for 4 of the 17 orphan products.

It is interesting that whereas the Breakthrough process is envisaged by the FDA as only to be granted to a subset of those products eligible for Fast Track status that especially merit it, 3 products in 2014—Blincyto (blinatumomab), Keytruda (pembrolizumab), and Zykadia (ceritinib)—gained the former status without being granted the latter. Perhaps the companies concerned just did not apply for it.

We suggest that some companies might have considered that Breakthrough status superseded or gave them no advantage over Fast Track status. Indeed, the FDA has even expressly stated that new drugs receiving Breakthrough therapy designation are eligible for all of the features of the Fast Track designation.[2] On the other hand, 4 orphan drugs approved in 2014 did have Fast

The 4 Different Expedited Approval Methods

Priority Review status is granted when the Center for Drug Evaluation and Research determines that a drug could provide a significant advance in medical care; it sets a target to review the drug within 6 months instead of the standard 10 months. There has to be potential for significant improvement in safety or efficacy. Unlike the other 3 methods, the US Food and Drug Administration (FDA) classifies all original new drug applications (NDAs) and biologics license applications (BLAs) for Priority Review whether or not the sponsor requests Priority Review.

Fast Track can speed new drug development and review, for instance, by increasing the level of communication FDA allocates to drug developers and by enabling CDER to review portions of a drug application ahead of the submission of the complete application. An unmet need has to be demonstrated to qualify.

Accelerated Approval allows early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments. To qualify, there must be a likelihood of meaningful advantage over available therapies.

Breakthrough Therapy designation includes all of the Fast Track program features as well as more intensive FDA guidance on an efficient drug development program. It is granted for a subset of fast-tracked products. Breakthrough status is designed to help shorten the development time of a promising new therapy. To gain this status, preliminary clinical evidence must indicate a substantial improvement over available therapies on a clinically significant endpoint. This method first appeared as an option taken for orphan drugs approved in 2013.

Table 1. Orphan drugs approved by the FDA in 2014

Brand Name	Generic Name	Indication	Company	Fast Track	Break-through	Priority Review	Accelerated Approval
Beleodaq	belinostat	T-cell lymphoma	Spectrum				
Blincyto	blinatumomab	Acute lymphoblastic leukemia	Amgen				
Cerdelga	eliglustat	Gaucher disease	Genzyme				
Cyramza	ramucirumab	Non-small cell lung cancer	Eli Lilly				
Esbriet	pirfenidone	Idiopathic pulmonary fibrosis	Roche				
Hetlioz	tasimelteon	Sleep-wake disorder	Vanda				
Impavido	miltefosine	Leishmaniasis	Paladin				
Keytruda	pembroli-zumab	Melanoma	Merck & Co				
Lynparza	olaparib	Ovarian cancer	AstraZeneca				
Myalept	metreleptin	Lipodystrophy	Aegerion				
Northera	droxidopa	Neurogenic orthostatic hypo-tension	Chelsea				
Ofev	nintedanib	Idiopathic pulmonary fibrosis	Boehringer Ingelheim				
Opdivo	nivolumab	Metastatic melanoma	Bristol Myers -Squibb				
Sylvant	siltuximab	Multicentric Castleman's dis-ease	Janssen Biotech				
Vimizim	elosulfase alfa	Mucopolysaccharidosis type IVA	BioMarin				
Zydelig	idelalisib	B-cell blood cancer[†]	Gilead				
Zykadia	ceritinib	Non-small cell lung cancer	Novartis				

[†]Chronic lymphocytic leukemia, follicular B-cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma.
Source: FDA[3] and other sources.

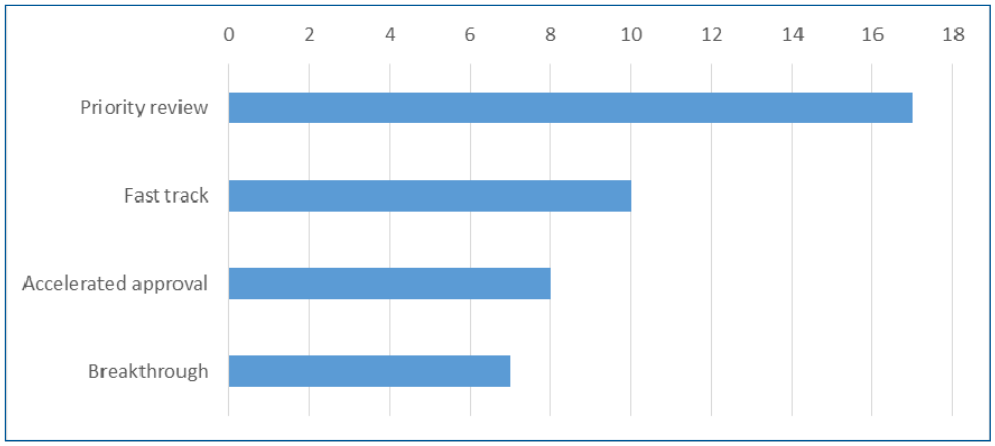

Figure 1. Expedited approval methods used by the 2014 cohort of approved orphan drugs.

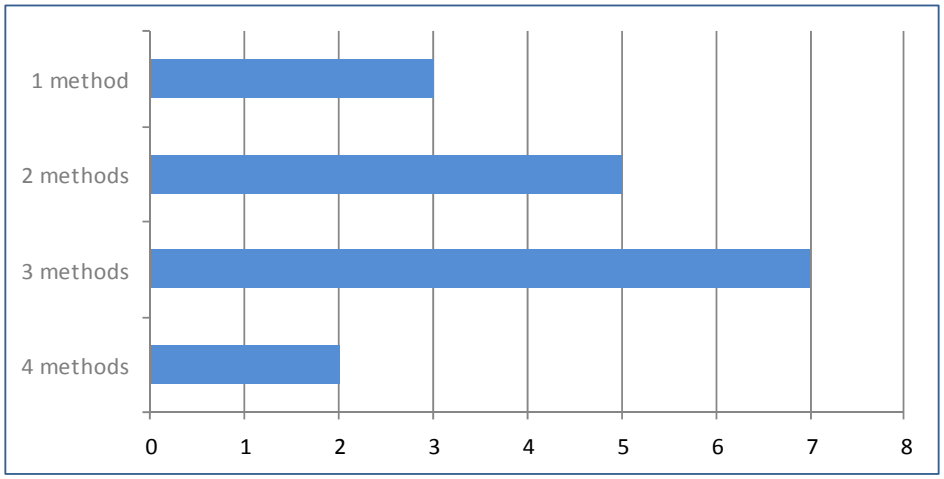

Figure 2. Number of expedited approval methods used by 2014 cohort of orphan drugs approved.

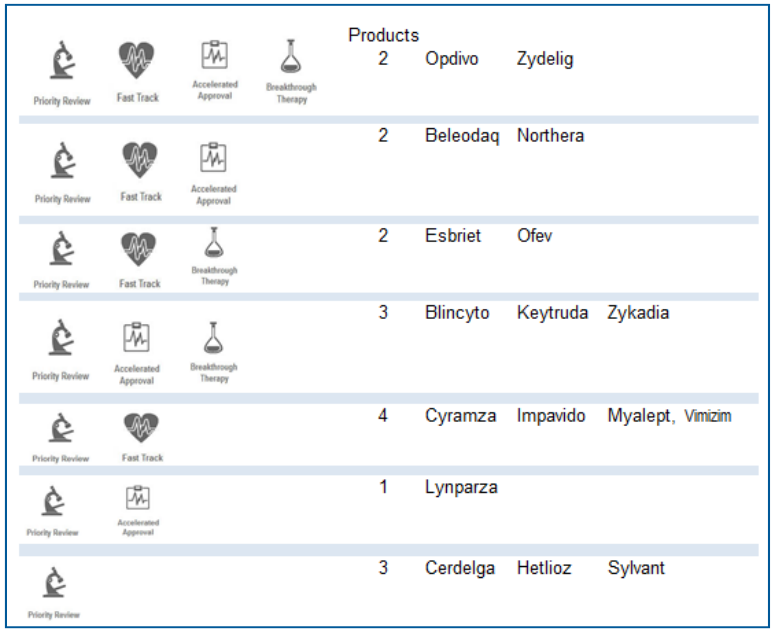

Figure 3. Expedited approval strategy combinations used for orphan drugs approved in 2014.

Track as well as Breakthrough status. These products were Opdivo, Zydelig, Ofev (nintedanib), and Esbriet (pirfenidone).

CONCLUSIONS

Current expedited approval methods employed by companies with successfully registered orphan drugs vary greatly. It is not clear why such a degree of difference exists. Also, it appears to us, on examining the data presented, that some companies might have benefited if they had applied for more of the 4 options. Kepplinger[3] and Jae[5] have thoroughly reviewed this perspective. We conclude that it is unlikely that the 4 different methods are being used by companies optimally.

A further factor could conceivably be contributing to this diverse usage. The summary criteria for the 4 expedited approval methods have much in common; however, it could be that the FDA is applying different degrees of stringency to similar approval criteria when it addresses eligibility for the different methods.[6]

The areas of overlap in assessing eligibility among the 4 methods would appear to offer the FDA opportunities to rationalize, unify, and thereby simplify these expedited approval systems—not just for orphans but for all types of drugs. It has already been proposed recently that the Breakthrough Therapy and Accelerated Approval processes be merged,[4, 5] and we believe this could be a sensible first step.

Another, specific area for resource savings relates to Priority Review. In 2014, for the first time, all 17 orphan drugs approved had been granted Priority Review status. We consider that there is now a case for waiving the Priority Review assessment process for all drugs granted orphan status and suggest that they should be granted Priority Review status automatically.

A more unified system that reduces the current duplication of assessment processes would reduce resources required by the FDA, which is important as use of the 4 expedited approval methods is increasing. It should at the same time be advantageous to companies making submissions, particularly those developing orphan drugs, whose resources—personnel, time, and financial—are often particularly limited.

ACKNOWLEDGMENTS

We wish to thank our colleagues at TranScrip Partners, Paul Branthwaite, Dr. Bob Milsted, and Louise Whitley, for their helpful comments, as well as Nicolette Theriault for graphics preparation.

CONFLICT OF INTEREST STATEMENT

JA and GT are both employees of Transcrip Partners; they do not have any financial relationship with the companies or products mentioned in this article.

REFERENCES

1. Developing products for rare diseases & conditions. US Food and Drug Administration Web site. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm. Updated February 26, 2015. Accessed June 3, 2015.
2. Orphan drugs in the EU: a record-breaking year. Regulatory Affairs Professional Society Web site. http://www.raps.org/Regulatory-Focus/News/2015/01/13/21063/Orphan-Drugs-in-the-EU-A-Record-Breaking-Year/. Accessed June 3, 2015.
3. Kepplinger EE. FDA's expedited approval mechanisms for new drugs products. *Biotechnol Law Rep.* 2015;34 (1):15-37.
4. Clinical development. TotalOrphanDrugs Web site. http://www.orphan-drugs.org/category/clinical-development/ Accessed June 3, 2015.
5. Jae VS. Simplifying FDASIA: the "fast track" to expedited drug approval efficiency. *Admin Law Rev.* 2014;66(1):173-198.
6. New drugs at FDA: CDER's new molecular entities and new therapeutic biological products. US Food and Drug Administration Web site. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm20025676.htm. Updated April 14, 2015. Accessed June 3, 2015.

Address Correspondence To:
Glenn Tillotson, PhD
2941 Honeymead Road, Downingtown, PA 19335 USA
E-mail: glenn.tillotson@transcrip-partners.com
Phone: (610) 383 5705