



Orphan Drug Designations in Ophthalmology

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Abstract

Purpose: To evaluate orphan drug designations within ophthalmology since passage of the Orphan Drug Act (ODA) and their ultimate availability and utility to the ophthalmic community.

Methods: The study design was a retrospective, observational review of orphan drug designations in ophthalmology.

Results: We identified 72 new ophthalmic drugs that received an orphan drug designation, of which four received Novel Drug Application (NDA) approval and all became commercially available, three for ocular and one for systemic indications.

Conclusions: This study suggests a low rate of commercialization of new ocular pharmaceutical agents with an orphan designation being approved for the original indication.

Keywords: Ophthalmology; Orphan drug act; Development; Treatments; Therapies

Introduction

Pharmaceutical development is a very long expensive and difficult task. Consequently, when a company undertakes the huge investment of personnel and financial resources to develop a new medicine they hope for commercial success to recoup costs as well as fund subsequent expensive research projects. Accordingly, new products typically chosen for development are those that will treat the broadest population allowing for potentially greater revenues.

This strategy, however, probably underserves many serious diseases which occur in small populations. To address this problem, in 1980s the United States Congress passed the 1983 Orphan Drug Act (ODA), which provides financial, regulatory and tax advantages to companies which will develop novel drugs to treat populations of $\leq 200,000$ Americans [1]. The act offers a number of specific potential advantages: including a grant provision, tax advantages, enhanced Food and Drug Administration (FDA) communications, and reduced Phase 3 requirements [2].

Since the time of the (ODA) passage, 3,346 total orphan designations have been granted [3]. These orphan designated drugs have had over 575 (17%) New Drug Application (NDA) approvals allowing potentially for commercialization [1].

Unfortunately, little information is available specifically regarding ophthalmic products that have received the orphan drug designation and their ultimate commercial availability to help treat less common ophthalmic diseases.

The purpose of this article is to evaluate the orphan drug designations within ophthalmology since passage of the ODA and their ultimate availability and utility to the ophthalmic community.

Methods

The study design was a retrospective, observational review of orphan drug designations in ophthalmology. We included designations from January 01, 1983 through December 31, 2011 (excluding designations after this date since NDAs would have limited time to be approved). We used the Orphan Drug List from the Health Resources and Services Administration website [3]. We also cross checked these designations on the Orphan Drug Designations and Approvals list on the FDA website [4].

Due to the non-interventional, non-clinical participant study design of this research Institutional Review Board/Ethics Committee approval was not required. Searches were conducted by one author and quality assurance by another author. Medical devices, stem cells, delivery systems that did not alter the pharmacologic efficacy of the molecule itself, compound products, and commercially available herbal products were excluded.

We included orphan designations from a new ophthalmic pharmaceutical product or an older approved systemically administered compound intended for a new ocular indication. We did not include medicines with prior ocular approvals. The following search terms were used: ophthalmic, eye, ocular, optic, retina, retinitis, cornea, glaucoma, conjunctiva, macular, blepharospasm, vision, pterygium, uveitis, retinopathy, blind, keratitis, corneal ulcer, fungal, and strabismus. Prior terms were searched from the designation: www.hrsa.gov.

More information was collected, including: commercialization of a company, FDA approval for orphan indication, and sponsors, using the following search engines: www.Google.com; www.accessdata.fda.gov and www.hrsa.gov

Results

The purpose of this article is to evaluate the orphan drug designations within ophthalmology since passage of the ODA and their ultimate availability and utility to the ophthalmic community.

We identified 72 new ophthalmic drugs that received an orphan drug designation since the inception of the ODA in 1983. Of these orphan medicines, four (6%) received NDA approval, each granted to the company submitting the application.

Of these 4 drugs receiving NDA approval, three (4%) were for the same ophthalmic indication as the original orphan designation

(cysteamine hydrochloride - a cystine-depleting agent; riboflavin ophthalmic solution & ultraviolet A - a photoenhancer; mitomycin - inhibits the synthesis of deoxyribonucleic acid) and one (1%) for another systemic indication (tasimelteon - an agonist at the MT1 and MT2 receptors). Of the four that received NDA approval, all (6%) became commercially available, three (4%) for ocular and one (1%) for systemic indications (Table 1). The 68 other ophthalmic drugs are listed in Table 2.

Generic/Trade name	Company filing NDA	Orphan indication	NDA approval indication
Cysteamine hydrochloride/ Cystaran	Sigma-Tau Pharmaceuticals, Inc.	Treatment of corneal cystine crystal accumulation in cystinosis patients	Treatment of corneal cystine crystal accumulation in cystinosis patients
Tasimelteon/ Hettioz	Vanda Pharmaceuticals, Inc.	Treatment of non-24-hour sleepwake disorder in blind individuals without light perception	Treatment for non-24-hour sleep-wake disorder
Riboflavin ophthalmic solution / ultraviolet A Photrexa Viscous	Avedro, Inc.	Treatment of keratoconus	Treatment of keratoconus
Mitomycin/ Mitosol	Mobius Therapeutics, LLC	Prevention of corneal sub-epithelial haze formation following surface ablation laser keratectomy	An antimetabolite indicated as an adjunct to ab externo glaucoma surgery

Table 1: Ophthalmic medicines receiving both orphan designation status and an NDA (New Drug Application)

Of all orphan designated drugs, 10 approvals were granted in the 1980s, 15 in the 1990s, 29 in the first decade of the 2000s and 18 since 2010 (**Figure 1**).

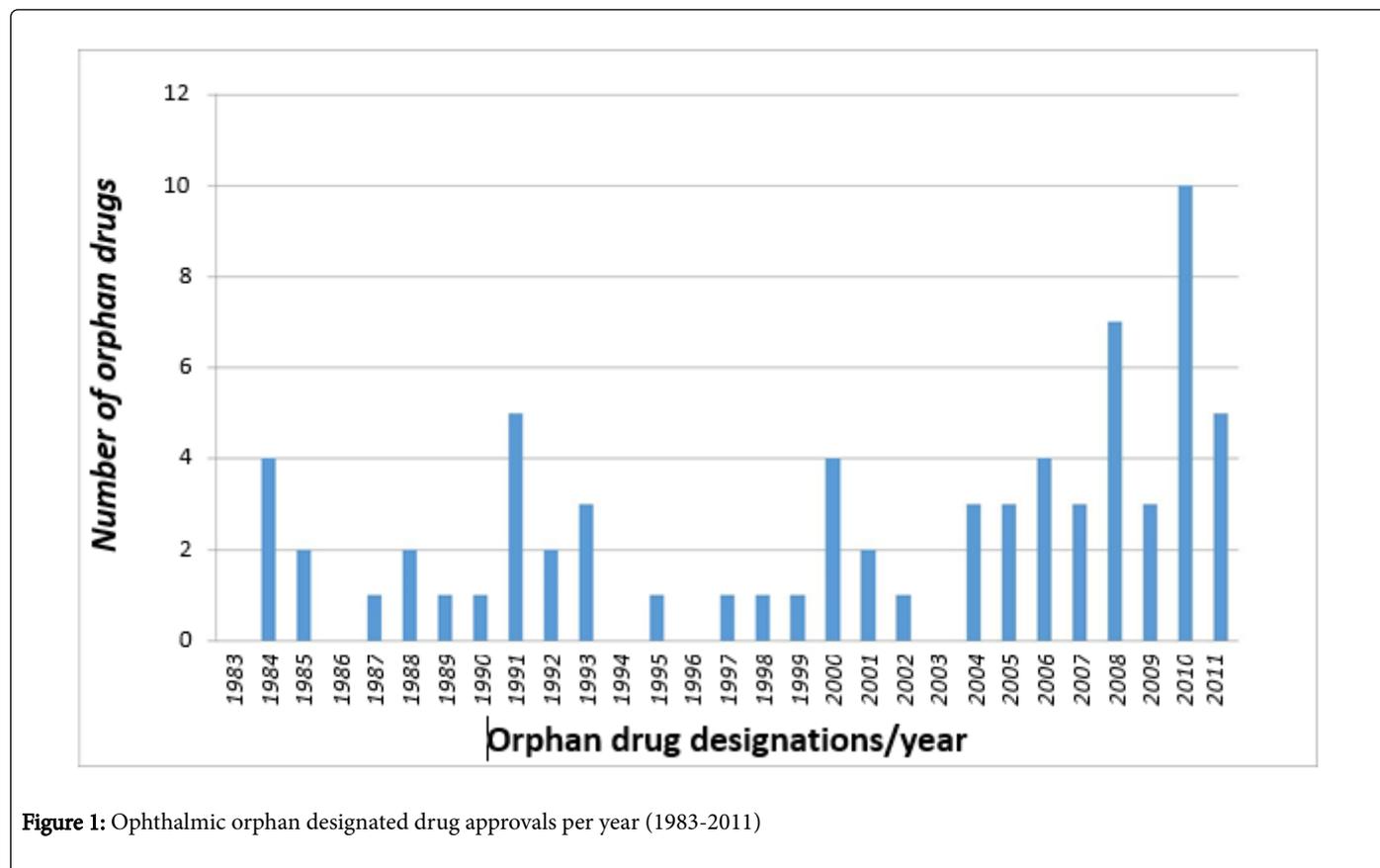


Figure 1: Ophthalmic orphan designated drug approvals per year (1983-2011)

Discussion

This study found that 72 ocular medications have received an orphan designation between 1983-2011. Of these, four (6%) received NDA approval from the FDA allowing commercialization of the medicine. This percent appears low compared to the 17% receiving NDA approval for all indications [1,2].

Each of the four orphan ophthalmic medicines receiving approval were commercialized. However, only three were for the original ocular orphan indication (4%) while the fourth was for a systemic indication.

It is difficult from these data to determine precisely if the orphan approvals were worthwhile for the FDA or the startup [3]. Further we did not have available sales figures for the three new ocular orphan medications. Considering the low NDA approval rate of ophthalmic intended orphan drugs, and the potential of changing to a non-orphan indication, it remains unclear if the administrative time and effort was beneficial for the Agency or the startup.

Why does an ocular orphan drug designation not appear to increase NDA approvals (4% in this study versus 13% general NDA approval rate in ophthalmology) [5]. We do not know for certain, but we can speculate over some reasons based on the potential advantages of the orphan designation: first, a major benefit to the startup of the orphan designation is the ability to negotiate a Phase 3 study with reduced criteria. However, this advantage would occur following the time period many startups would have already licensed their medicine. Second, orphan designation cost advantages to the startup are small early in development with most of the benefits coming later, potentially after the medicine has been licensed. Third, the whole financial and development package may not be enough benefit to bring these medicines to commercialization, especially in the early startup phase. Last, an orphan medicine will by definition have a limited sales market and so the projected financial profile may inhibit further development.

Nonetheless, orphan drug designation may have advantages for the startup by alleviating some early funding costs, speeding product development, as a sales point to a potential licensee of the FDA's interest in the medicine, and evidence of future financial and development incentives under the orphan drug program later in development or post commercialization [6-8].

This study suggests a low rate of commercialization of new ocular pharmaceutical agents with an orphan designation being approved for the original indication.

More information is needed regarding the final commercial outcome of FDA approved orphan drugs, the reason why so many did not receive NDA approval, and more precise comparisons to non-orphan drugs in the development process.

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