

Orphan Drugs: Future Viability of Current Forecasting Models, In Light of Impending Changes to Influential Market Factors

by

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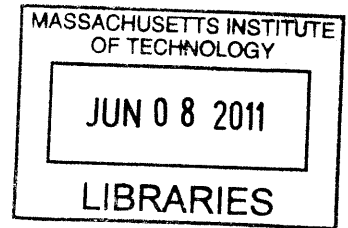
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Interviews were conducted to establish a baseline for how orphan drug forecasting is currently undertaken by financial market and industry analysts with the intention of understanding the variables typically accounted for in such a model. A literature search formed the basis of subsequent interviews conducted with experts from industry, payers, providers, legislators, patient groups, and the FDA. Discussion then focused on elements of the market which are poised to change in the short-term, how such changes might be reflected in existing models, and/or how these models may instead need to be modified to adapt to the new environment.

We hypothesized that impending changes in the healthcare sector would indeed impact the legitimacy of current forecasting models, and that significant changes would need to be introduced to account for these new market forces. Our hypothesis, however, was not confirmed, in that although much of the literature and, indeed, public outcry over rising healthcare costs in general and drug prices in particular make a strong case for implementing changes in the orphan market via payers, government, or other actors, an assessment of healthcare experts regarding market changes over the next five years revealed a general consensus that meaningful change will likely not occur during this timeframe for orphan products, with the exception of a possible increase in pharmacoeconomic requirements for drugs which are only marginally effective. Thus, current orphan drug forecasting models constructed for use by financial and industry analysts correctly avoid discounting for these potential changes, as they will likely not face significant changes in the US until closer to a ten year time horizon. Potential exceptions to this conclusion depend on implementation and regulatory treatment of the fields of personalized medicine and gene therapy, as developments in these areas may closely interact with existing orphan drug legislation. Our results have significant implications for all companies and stakeholders entering or currently operating in the orphan market, and open the door for further quantitative and qualitative analysis.

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Dedication

To my wife, Rebecca, for her constant and unflagging love, support, and inspiration.

To my parents, Dr. George and Barbara, for providing me with endless opportunities and unbounded support.

To all my advisors and mentors at both MIT and Harvard, who gave of their time and energy to help make my journey here a successful one.

Acknowledgements

One of the primary draws of healthcare to a professional is the notion of being able to have a significant impact on the lives of others, whether participating through a role in R&D or on the commercial side. Nowhere is this impact more clearly felt and appreciated than with rare diseases. The individuals who suffer from these ailments have few places to turn, and the companies which choose to help them can be proud of having made a very clear difference in their lives. I chose a thesis topic which explores the future of this process, trying to understand what form orphan drug access and reimbursement will take in the years to come as I begin my career in the healthcare space.

I would like to express my sincere gratitude and appreciation for the guidance provided to me in this process by my thesis advisors, Professor Teo Dagi and Parag Meswani, helping me to define the scope and direction of my research this past year. Additionally I would like to thank the analysts and experts who generously lent of their time for interviews and thought direction.

Over the past three years, I feel that I have grown tremendously both in education and experience, helping to prepare me both personally and professionally for the years ahead. I would like to acknowledge those who have helped me along the way through teaching and mentoring I have received at Sloan, MIT, HMS, and MGH over my time at BEP. Aside from my thesis advisors, I would like to thank my fellow BEP students who have taught me so much, Prof. Richard Cohen, Prof. Ernie Berndt, Prof. Carl Berke, Prof. Howie Golub, Prof. Stan Lapidus, Prof. Richard Anders, Traci Anderson, and members of the BEP Advisory Board for an invaluable experience.

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Table of Contents

Abstract.....	2
Dedication.....	4
Acknowledgements	5
List of Figures.....	8
Chapter 1: Introduction	9
Chapter 2: Background	11
Orphan Drug Act of 1983.....	11
Industry Response to the New Legislation	13
Rising Stakeholder Concerns	14
Industry Reactions	17
Foreign Approaches to Cost Issues.....	22
Chapter 3: Thesis Objective and Methodology	25
Thesis Objective	25
Review of Existing Literature	25
Interview Guides.....	26
Selection of Interview Participants.....	28
Chapter 4: Interviews and Results.....	30
Summary of Analyst Interviews.....	30
Summary of Expert Interviews	33
Expert Interview Conclusions	34
Discussion of Specific Interview Questions	35
Chapter 5: Discussion.....	45
Implications.....	46
Limitations	47
Future Research.....	48
Chapter 6: Additional Challenges	50
Generics Marketed as Orphan Products.....	50
Government Recommendations.....	51
Risk-Sharing Agreements.....	52
Global Impact.....	53

Chapter 7: Conclusions 54

- Challenges for Regulators and Legislators..... 54
- Challenges for Payers..... 55
- Challenges for Patients, Patient Advocacy Groups, and Providers 56
- Challenges for Industry..... 56

Appendix A: Interview Contacts 57

Appendix B: References..... 58

Additional Notes 62

List of Figures

Figure 1: Orphan Drug Act key benefits overview and legislative history.....	13
Figure 2: Key trends driving large pharmaceutical companies toward orphan product development.....	20
Figure 3: Cost burden shift toward consumer payments for specialty products	22
Figure 4: Organizations represented by interview respondents	29
Figure 5: Breakdown of interview respondents by sector.....	29
Figure 6: Select risk sharing deals in biotech / pharma.....	52

Chapter 1: Introduction

Orphan drugs occupy a unique niche in many pharmaceutical and biotech portfolios, and maintain a perceived value proposition which is disproportionately high when compared with other innovative products. The reasons for this perception relate primarily to increased revenue driven by very high margins and market exclusivity, and by the public relations boon of helping an underserved population of patients. The revenue benefits enjoyed by the industry stem directly from the Orphan Drug Act, which, passed in 1983, created a wide range of incentives to encourage drugmakers to dabble in a market for diseases which would not otherwise justify such an investment.

However, in recent years, there has been call for reform across the healthcare landscape, and nowhere are the cries as intense as in the orphan world, where emotion plays almost as significant a role as other market factors. Patients, along with providers and advocacy groups, clamor for newer, better, innovative treatments for more diseases, while payers attempt to manage costs and to pay only for more efficacious treatments. This emphasis on “pharmacoeconomics” is gradually growing in a number of forms across the world, as both government and commercial payers begin to account for ever-rising costs in a macroeconomic downturn. On top of these concerns lie the regulatory and legislative bodies on whose decisions ultimately turn approval, access, and reimbursement to orphan drugs, and which, at least in the legislative case, can be motivated at times by public opinion to capricious change, causing stakeholders no shortage of uncertainty and concern.

Based on these observations, we hypothesized that the industry is poised to change in the short term, whether due to a shift in the primary value proposition or on account of a legislative / regulatory amendment, and that current models used to predict orphan drug revenues and costs would thus need to be amended in the near future to account for the impact such changes will inevitably have on existing pricing, reimbursement, and incentive schemes.

The primary purpose of this thesis is to examine whether the current incentive structure for orphan drugs is likely to persist unchanged given upcoming developments in healthcare policy reform, pharmacoeconomic demands, and the more general emphasis on cost containment. We further endeavor to empirically consider what specific effects such changes might have on revenues, costs, and incentives in the orphan product space, using industry and financial

forecasting models as a guide to the way these elements are currently represented. As the thesis evolved, it became apparent that any attempt to categorize the short-term future of the orphan drug space would be woefully incomplete were it not to include an analysis of the roles of individual stakeholders in defining this future. As such, we ultimately suggest the unfolding role each set of stakeholders must accept in emerging industry dynamics in order to collaborate in developing a more sustainable value proposition in years to come.

This thesis is organized in the following manner. We begin with a comprehensive look at the background and history of orphan drugs, considering, among other things, the legislative history and implications of proposed changes to the Orphan Drug Act over the years. We next turn to more recent times, examining successes and challenges encountered in succeeding years by both companies and other industry stakeholders, and we survey cost containment measures undertaken by foreign governments to try to reign in rising healthcare expenditures. Having thus gained a more significant understanding of the primary factors affecting the current market for orphan products, we discuss in detail the methods used for evaluating our hypothesis, before launching into a comprehensive analysis of our results. We subsequently consider implications and limitations of our work, thereby laying the groundwork for future studies, and we then briefly discuss the likely impact of several additional challenges facing the industry. We conclude with a summation of the lessons garnered through this analysis, and describe some of the challenges individual stakeholders involved in orphan drugs will inevitably face in the coming years, as the industry inexorably continues to evolve.

Chapter 2: Background

Orphan Drug Act of 1983

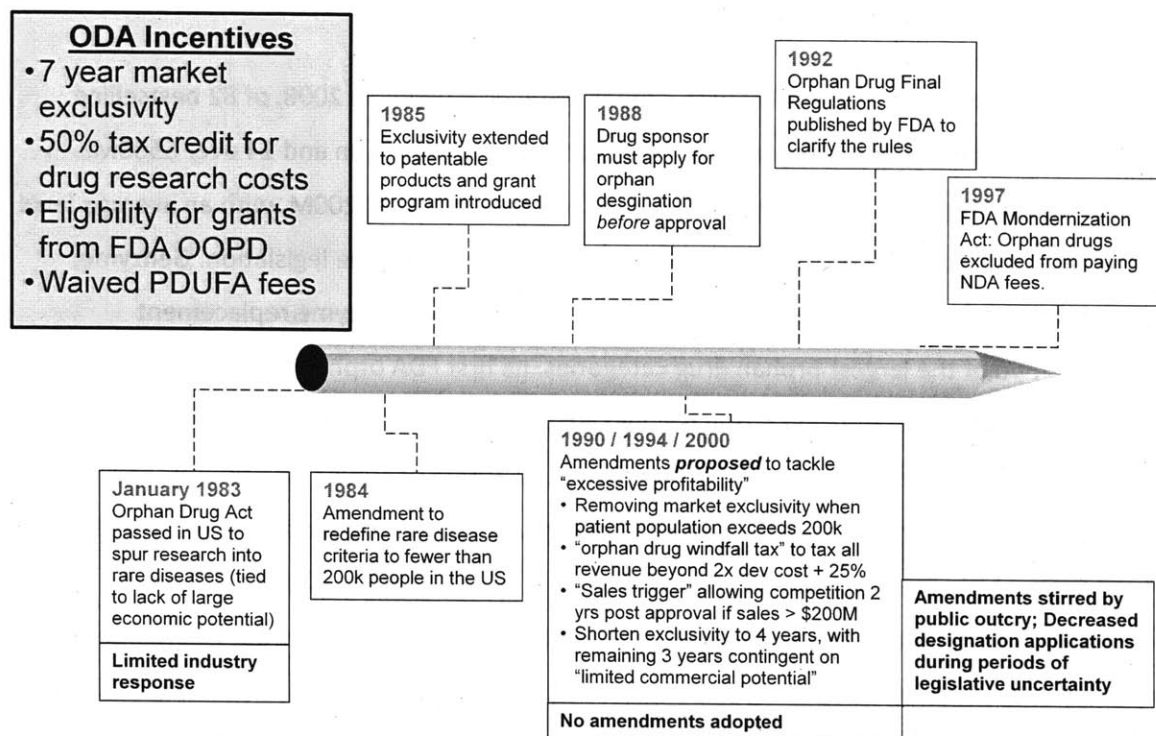
In the early 1900s, new treatments for many diseases were being developed at federally operated labs and by non-profit organizations. By the early 1960s, however, the landscape had shifted in favor of private, for-profit pharmaceutical companies providing most new chemical entities and virtually all approved drugs, while federal and academic institutions focused more on basic research and clinical studies⁴⁰. This system worked very well for diseases affecting large groups of patients, as the high costs associated with bringing a drug to market could be offset by addressing a large market size (whether with greater or lesser efficacy). However, patients with rare diseases were often simply out of luck in looking for treatment, as pharmaceutical companies had little incentive to develop drugs for these small markets. Consequently, in the decade leading up to the orphan drug legislation passed in 1983, only 10 products which qualified as orphan indications reached the market²⁸. Even molecules which had already been discovered and may have been efficacious for treatment of a rare disorder were left on the shelf or “orphaned”, lacking a sponsor to conduct the research necessary for gaining FDA marketing approval. Making matters worse, many of these products were unpatentable⁴⁰, further exacerbating the dearth of development in this area. Spurred by the pleas of patient advocacy groups, Congress unanimously enacted the Orphan Drug Act (ODA) in 1983 to provide economic incentives toward the research and development of drugs for rare diseases. As Congressman Henry Waxman (D-CA) eloquently put it, *“They are like children who have no parents, and they require special effort.”*

The original legislation attempted to provide incentives while reigning in the possibility of abuse of the system for corporate profit. The primary incentives included a 7 year market exclusivity period and a 50% tax credit for drug research costs. However, the legislation also specified that a “rare disease or condition” which qualified for orphan designation be tied directly to the lack of large economic potential. This ambiguity discouraged pharmaceutical makers from taking full advantage of the incentives and in the first year of the program (1983-1984), the FDA received only 15 requests for orphan designations. Congress thus amended the legislation in 1984 to redefine rare diseases as those illnesses which affect fewer than 200,000 people in the US or for which there is “no reasonable expectation of recovering development costs through US sales.”

At that time, Congress noted the potential for abuse of the system, namely using the monopoly status granted by market exclusivity combined with very high monopolistic pricing to create blockbuster drugs on the back of taxpayer incentives, but ultimately decided that this was a necessary risk to help induce industry participation⁴⁰. The ODA has subsequently been subjected to multiple modifications, some larger than others, which have contributed heavily to the state of the industry today. In 1985 the legislation was amended to allow market exclusivity for patentable products as well and allowed for federal grants for clinical evaluation of orphan-designated drugs. A 1988 amendment required a sponsor to apply for orphan designation *before* submitting an application for marketing approval. In 1992 the FDA clarified the regulation (especially with regard to what constitutes a violation of marketing exclusivity), by publishing the Orphan Drug Final Regulations². In 1997, as part of the FDA Modernization Act, orphan drugs were exempted from paying new drug application fees (a fee which is now over \$1M). The Rare Disease Acts in 2002 ensured that sufficient budget existed for the Office of Rare Diseases and increased funding for the FDA Orphan Products Research Grant Program.

Just as important, perhaps, as the changes which have occurred in the legislation over the last 30 years are the changes which have not occurred. Spurred by popular sentiment, proposed amendments to the act in 1990, 1994, and 2000 have taken on the concept of market exclusivity and “excessive profitability”, offering changes such as removing market exclusivity when patient population exceeds 200,000 (as occurred with early drugs for AIDS such as AZT), creating an “orphan drug windfall tax” which would tax all revenue earned on an orphan product beyond twice the development cost plus 25%, creating a “sales trigger” which would allow competition into the market just two years after approval if sales exceed \$200 million, and reducing market exclusivity to four years, with the following three years contingent on demonstrating “limited commercial potential”. Pharmaceutical companies protested vehemently in each case, arguing that any reduction in the power of the available incentives would strongly decrease orphan drug R&D and detract from the original purpose of the bill, thereby harming patients. Indeed, during the time when Congress was debating these amendments, designation requests for orphan products dropped significantly⁴⁹. While the amendments ultimately failed to become law in each instance, the repeated and determined nature of the attempts to reform the law (in the case of the 1990 amendment, the changes actually passed through Congress only to be vetoed by President Bush) would seem to indicate that given enough public pressure and willpower in Congress, changes may one day indeed occur.

Figure 1: Orphan Drug Act key benefits overview and legislative history



Industry Response to the New Legislation

The industry response to orphan drug incentives in the US has been impressive to say the least. Dr. Tim Cote, head of the Office of Orphan Product Development (OOPD) at the FDA contends that, "there is no question that the Orphan Drug Act is without a doubt the single most successful piece of legislation that has ever been passed in human experience." Since the Act's inception in 1983, there have been over 2200 requests for orphan designation in the US with over 360 drugs reaching marketing approval, resulting in treatments for approximately 200 rare diseases (as of the end of 2010)³⁴. Additionally, the entire biologics industry effectively grew up out of treating orphan indications, creating tremendous economic growth along the way. As of 2007, biologics comprised approximately 64% of the US orphan drug market, and new orphan drugs / indications made up 2/3 of all biologic approvals in 2008-2009^{1,34}. As an added benefit, many research initiatives which originally took aim at orphan indications have spun into some of the most successful treatments of all time. Statins, for example, which generated roughly \$25Bn in revenue in 2009, actually got their start based on research meant to address an orphan condition known as homozygous familial hypercholesterolemia⁵². Many countries have implemented reform in the orphan space since that time, attempting to emulate the US success

in spurring innovation. Japan enacted its law in 1993, Australia adopted similar legislation in 1997, and the EU followed suit in 2000.

Industry has found financial success with orphan products as well. In 2008, of 82 bestselling orphan drugs from the top 50 companies, nine had sales of over \$1bn and 14 over \$500M. Regarding the drugs themselves, more than 50% had sales of over \$200M, with an average level of \$470M²⁸. Individual companies have also grown and thrived on the legislation. Genzyme, started in 1981, focuses on disease areas including oncology and enzyme replacement therapies, two of the largest orphan drug categories. Its first FDA orphan drug approval came for Ceredase, used to treat Gaucher's Disease, and coupled with high price tags for many therapies, (Cerezyme has an average sales price of upwards of \$200,000 per year²⁸) it has ultimately built its portfolio into revenues of \$4.5Bn in 2009, leading to a buy-out by Sanofi Aventis in 2011 for over \$20Bn. This success considerably exceeded analysts' predictions as turning formerly fatal diseases into chronic conditions served to increase the number of patients above previously recorded prevalence levels. Other successful companies have followed suit, including Shire, Celgene, Biomarin, and Actelion. Many of the drugs which began life as orphan products have subsequently become blockbusters through off-label use or expansion to other indications. Botox, marketed by Allergan, was originally approved for dystonia (a neurological disorder affecting movement), which qualified it for orphan status. It has since become one of the company's biggest revenue streams (over \$1.3Bn in sales in 2009), due almost entirely to its use for cosmetic purposes. Gleevec, which was unanimously approved as a treatment for chronic myeloid leukemia in a record-breaking 2.5 months due to its tremendous treatment efficacy, has since been approved for at least 8 additional indications, and produced almost \$1.3Bn in US sales in 2010. As of 2009, of 18 blockbuster drugs approved only in orphan indications, all but 4 were approved for multiple indications or involved significant off-label use⁵².

Rising Stakeholder Concerns

Yet it is a combination of this very success and several other unintended and more deleterious consequences of the orphan drug legislation which has catalyzed public opinion, occasionally riled Congress, and caused other industry stakeholders such as payers, physicians, and patient advocacy groups to ponder mechanisms for fighting back against rising costs. It is commonly understood that US healthcare expenditures have been rising rapidly in recent years. In 2009,

national health expenditures famously accounted for 17.6% of US gross domestic product, averaging over \$8,000 per capita. Of this expenditure, retail prescription drugs accounted for roughly \$250Bn, or over 5% of total national health spending, and this number is rising as well²⁵. Specialty drugs, including those with orphan status, represent an even more rapidly expanding cost, with a growth rate of almost 20% in 2010³³. These rising expenses, set against a backdrop of depressed macroeconomic factors, have caused the high price tags of many specialty and orphan drugs to become a source of particularly vehement popular ire. The public argues that taxpayers are subsidizing corporate success and greed (although in fairness, blockbusters in the orphan space are still relatively rare²⁸) through the orphan drug program incentives, while patients suffering out of pocket expenses (a typical coinsurance plan can require a patient to stake 20% of the cost of a drug) feel that even if much of the profit is plowed back into R&D, they are being asked to carry an unfair load of the research funding for other diseases. As one industry leader contended, "From a patient perspective, they don't appreciate that Genzyme was built on their backs." A Kaiser public opinion poll in 2008 found that 79% of those polled felt that the cost of prescription drugs was unreasonable, and an identical 79% cited the quest for high profits on the part of drug companies as bearing primary responsibility for those prices²². Physicians and patient advocacy groups such as the National Organization for Rare Diseases (NORD) are concerned about rising costs if they lead to decreased patient access to drugs, but they are equally concerned about pushing back too hard on industry and decreasing the innovation levels which have dramatically improved the lives of countless patients since the legislation went into effect. Payers have historically been generally unconcerned with rising prices on orphan drugs because they made up such a small part of the overall drug pie (roughly 5% in 2009²⁸). However, the rise in initial prices from manufacturers, coupled with a feared barrage of orphan products coming through pharma pipelines to treat rare oncology conditions, now has fully captured payers' attention. Orphan designations increased at a CAGR of 17.7% between 2002 and 2008²⁸. A 2006 meeting of the Academy of Managed Care Pharmacy listed the rising cost of orphan drugs as one of the industry's primary concerns for coming years¹⁹. This fear is coupled with a perceived impending wide-spread adoption of biomarkers and personalized medicine, which could in theory serve to create unique drug cocktails for every individual. Would each of these cocktails thus be considered an orphan product? The government has also expressed concern with the rising costs of pharmaceuticals, while continuing to recognize the importance of encouraging industry involvement in orphan product

development. On July 24, 2008, in testimony before the Senate Joint Economic Committee, Madeline Carpinelli of the PRIME Institute presented findings showing extraordinary price increases of 100% or more in the pharmaceutical market (some as high as 3000%), and noted cases of orphan drugs which have typically “flown below the radar” demonstrating unwarranted price increases as well⁴. This testimony generated a slew of Congressional backlash. As Senator Amy Klobuchar (D-Minn.) fumed, "Something's going on, and I don't think it's the law of supply and demand. This seems to be simple price gouging to me."²¹ A Government Accountability Office report released in February 2011 further emphasized the government’s concern over drug price increases eclipsing other medical expenses⁴⁹. With the expansion of Medicaid coverage brought about by healthcare reform, government sources are looking with increasing skepticism at prices for specialty products and may now consider actions previously thought to be anathema in the US healthcare system in order to effectively curb such costs.

In addition to stakeholder concerns, several characteristics of the Orphan Drug Act lead to ethical situations which may result in pushback or a call for change. In June 2009, Genzyme was forced to close its plant in Allston, Massachusetts, when viral contamination was discovered. In November 2009, the FDA found foreign particles consisting of steel fragments, non-latex rubber, and fiber-like material in vials of Cerezyme and Fabrazyme, further distressing supply. Orphan drug laws protecting marketing exclusivity had discouraged other drug makers from pursuing treatments for diseases like Fabry, and the result has been a shortage such that many patients only have access to a third of the drug supply they would normally receive, prompting multiple lawsuits and attempts to break the drug’s patent protection²⁴. More generally, the marketing exclusivity clause often leads to a “race to market approval”, leading multiple companies to pursue research into a treatment which only one can end up marketing, and thus potentially diverting funds from other patients in need while also driving up prices. In 1999, IVAX and BMS raced to get a drug approved for Kaposi’s sarcoma, a rare virally-caused tumor, with IVAX making a less-costly generic version of the same drug. BMS beat IVAX out in applying for marketing approval by 6 days, resulting in the drug Taxol (paclitaxel), which garnered over \$1.5Bn in sales in 2000. Additionally, despite healthcare reform removing lifetime caps on insurance plans, and although many companies offer patient assistance programs to help those unable to afford out of pocket costs, many of those patients who are deemed “able to pay” face serious financial difficulties, and still others do not get the assistance they need. A Kaiser study

in 2009 found multiple examples of patients who ran up very significant bills for cancer treatment and were in danger of losing access to necessary drugs. Finally, as orphan drugs need not be novel new compounds, industry has at times found ways to gain approval and an orphan designation for existing treatments, causing an extreme price bump and widespread condemnation from the public and the media. Examples of this methodology include Oxandralone, an AIDS drug in the 1990s, as well as Colcrys, Achar Gel, and most recently, a drug called Makena used to treat the risk of pre-term labor. Makena, marketed by KV Pharmaceutical Co, was previously made by compounding pharmacies as 17P (hydroxyprogesterone) and was used off-label for years for the same indication. By virtue of its approval and orphan designation, the drug price spiked from between \$5 and \$15 per shot to \$1500 per injection, resulting in total costs per patient of up to \$30,000⁶. Indeed, Senator Amy Klobuchar, the same senator who responded vehemently to the 2008 testimony from the PRIME institute on drug price increases, has sent a letter to the FTC calling for a probe into egregious pricing of Makena⁵¹. The FDA responded in an unprecedented letter informing compounding pharmacies that it will not take enforcement action against them if they continue to make the drug, in direct contradiction to a letter sent earlier by KV⁹. The company subsequently responded by slashing the price more than 50%, although it remains unclear whether this move will pacify the intense patient, provider, and political outcry⁴⁶.

Industry Reactions

Industry passionately rejects these criticisms and contends that while there are at times cases where blockbuster drugs are created from orphan beginnings, these cases are rare and are offset by the extraordinary risk taken in developing treatments for extremely small patient populations. Additionally, as Dr. Cote points out, "A lot of orphan products are downright cures. It makes us all feel really good to be able to make a downright cure. That is a rare thing in medicine." As such, few people complain about the cost of drugs like Gleevec, which has a 5 year survival rate among CML patients of roughly 90%-95% [data from Gleevec website]. Secondly, expansion to other indications remains one of the primary reasons companies are willing to dabble in such a risky market in the first place. A Datamonitor report in 2009 estimates that, "The sales achieved from a single orphan indication alone can offer little incentive for a manufacturer given the small market size. The real monetary gains are achieved through expanding the number of indications of an orphan drug once at market either through targeting

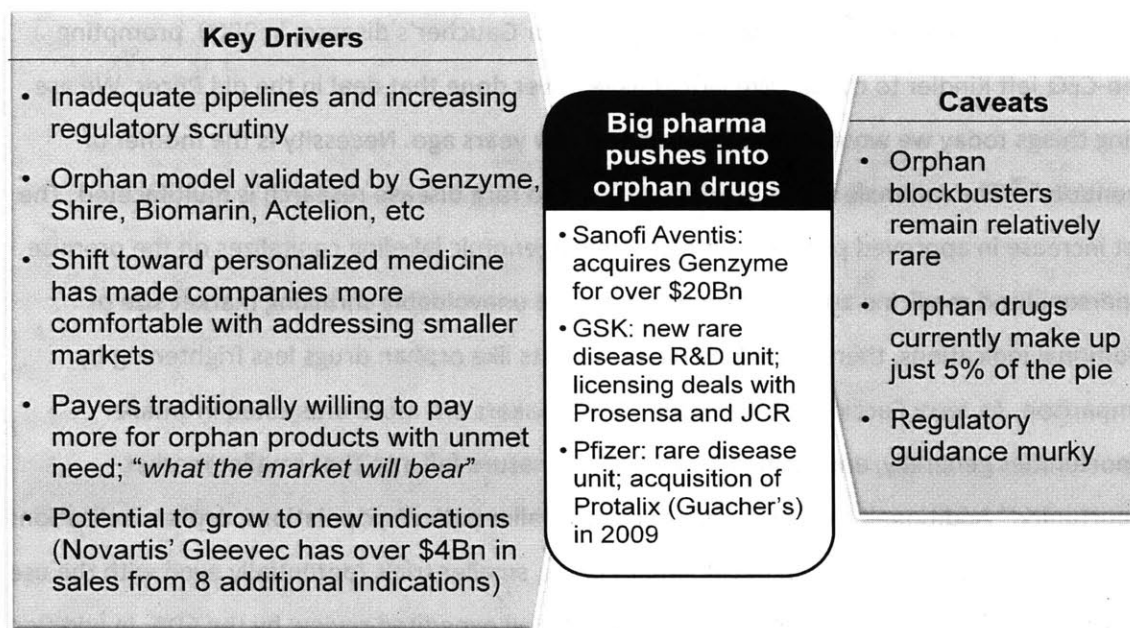
multiple indications... or by expanding into other orphan indications with larger patient populations.” Similarly, Mark Fishman, President of Novartis Institute for Biomedical Research, pointed out, “If we understand the mechanism in a narrow or niche indication then of course we hopefully will be able to extend it out to other diseases which share underlying mechanisms.”²⁸ By this measure, companies argue that pricing drugs at a higher rate for niche indications is the only way to recoup the massive costs which go into R&D and clinical trials for every drug candidate, especially taking into account the large risk of failure. Even drugs which were reformulated for orphan indications out of generic substances have undergone extensive safety, efficacy, and dose determination trials, as well as FDA approval and marketing, at significant expense to the drug’s sponsor, for which they deserve to be reimbursed.

One other trend within industry deserves to be noted here as well. Historically, large pharmaceutical companies have always had a hand in the orphan market, and many continue to do so. However, the traditional pharma model does not necessarily lend itself easily to this market. For one thing, pharma has traditionally excelled at maintaining and incentivizing extensive sales forces designed to carry out large-scale marketing campaigns for new and existing products. This methodology places the focus squarely on physician contact over patient interaction. Orphan indications, by their nature, require intensive *company* - patient interaction, whether through assistance programs, education, or support for all aspects of disease management. Success is measured by acquiring and retaining individual patients, not geographic segments of physicians. In orphan drugs, “the heart and soul of the commercial [effort] is the patient community. Big Pharma needs to transform the commercial model, and that is no small undertaking,” says Jerry Cacciotti, VP at IMS Health²⁸. Additionally, limited understanding of the market may hinder development efforts. Perhaps more importantly given the current economic environment, large companies with billions in their pockets are easy targets for negative PR which may result from the high pricing which typically accompanies orphan products. Although this effect is somewhat offset by the positive publicity inherent in treating diseases with a large unmet medical need, these factors cumulatively have historically held large pharmaceutical companies back in their pursuit of new development opportunities.

Of late, however, big pharma has announced plans to get involved with orphan diseases in a more substantial way. Sanofi Aventis purchased Genzyme this year for over \$20Bn. GSK launched a new unit in 2010 focused on R&D for rare diseases, following a licensing agreement

with Prosensa and a follow-up deal with JCR Pharmaceuticals Co, a Japanese maker of enzyme replacement therapies. Pfizer has an active rare disease unit and purchased Protalix, an Israeli company developing a plant cell based treatment for Gaucher's disease, in 2009, prompting then-CEO Jeff Kindler to claim, "We would have never done that deal in the old Pfizer. We are doing things today we would never have done a few years ago. Necessity is the mother of invention."²⁸ The rationale for this sudden influx into rare disease research is multifaceted. The vast increase in approved products with pharmacogenomic labeling capitalizes on the promise of personalized medicine and has demonstrated the unavoidably shrinking market size of traditional indications, thereby making niche markets like orphan drugs less frightening by comparison. As Jerry Cacciotti pointed out, "Drug makers are more interested in smaller opportunities generally, and orphan drugs by their nature fall into that smaller market opportunity." Additionally, by virtue of affecting smaller patient populations, orphan indications traditionally entail lower clinical development costs, smaller trials (potentially even with the use of surrogate endpoints and non-placebo controls), and expedited review by the FDA, in addition to the incentives affiliated with the Orphan Drug Act discussed above. Safety profiles for orphan drugs are also less relevant, as the benefit-risk ratio in cases where no other treatment exists, combined with strong patient advocacy, almost always effects a scenario whereby non-life threatening side effects fall by the wayside. All of these factors, however, pale in comparison to the high margins that orphan drugs traditionally return. Pricing has historically been based on "what the market will bear", which has resulted in the potential for significant earnings, even based on lower sales in a smaller market. This pricing, though, as with traditional pharmaceutical products, is coming under increasing pressure from multiple stakeholder angles, as Jacqueline Kosekoff, CEO of United Healthcare subsidiary Prescriptions Solutions, succinctly described it, "I suspect something is going to happen. Whether it is the orphan drugs that are the straw that breaks the camel's back or whether it's the huge barrage of oncologic drugs that are coming our way that is going to be the straw, I don't know. I just see it."²⁸

Figure 2: Key trends driving large pharmaceutical companies toward orphan product development



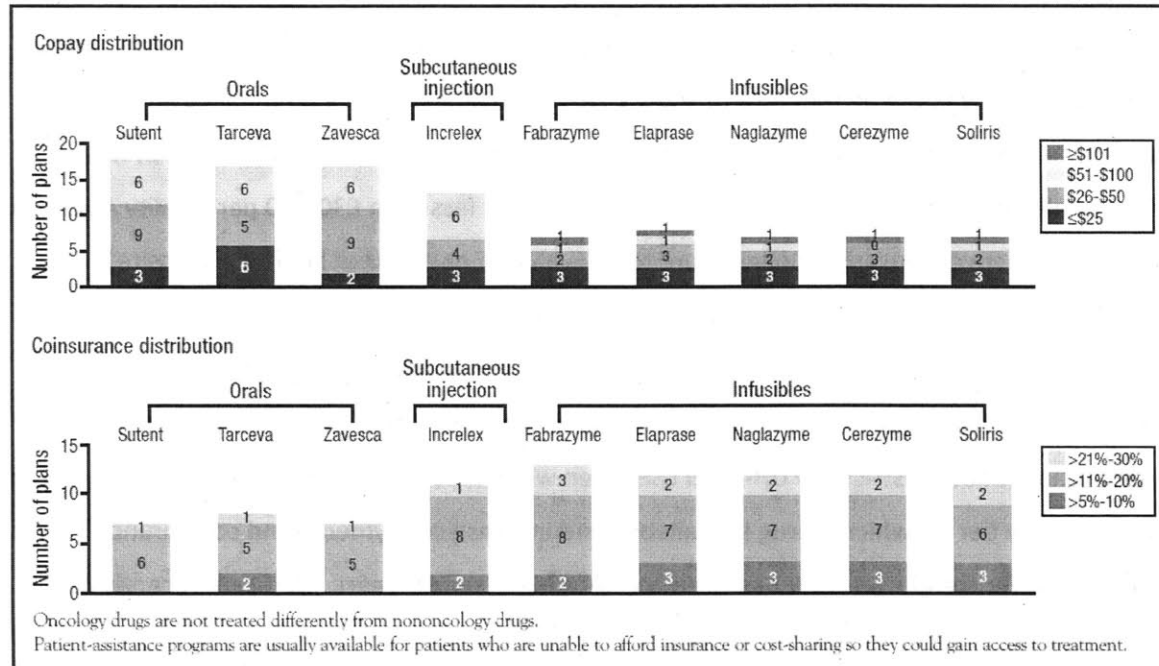
Changing Paradigms

The confluence of factors driving up costs thus coincides with decreasing tolerance for such costs in the current macroeconomic environment and has prompted a number of different approaches to reigning in healthcare drug spending, which in turn may affect orphan drugs as well. The first (and some would argue least likely to succeed) mechanism has been on the legislative front. As mentioned above, legislation to shorten the exclusivity period, tax “excessive” profitability, or at least claw-back tax subsidies for very successful drugs has repeatedly been introduced in Congress only to ultimately fail. Bills were introduced in 2011 which take on drug prices more generally by attempting to shorten patent expiration on biologics to seven years from twelve years and to allow importation of FDA approved therapies from other countries. The former would seek to hasten generics coming to market, and the latter, which has been facetiously dubbed “The Death of the Pharmaceutical Industry Act” by some in the media, attempts to balance the higher prices paid in the US against those paid in other countries. Neither measure stands a large chance of success, but the implications are clear. Washington, reflecting popular sentiment, is not immune to external pressures and desires to curb retail drug prices in any way possible. A second mechanism, embraced by some payers, is to attempt to more carefully assess outcomes to determine efficacy of the care

provided. This pharmacoeconomic focus can come in several flavors. The simplest application is to require a demonstration of clinical value through measurable outcome measures, thus showing that a drug is actually effective in achieving its goals within a target population. More drastically, a drug could be required to show cost-effectiveness from a point of view of valuing human life. The UK's National Institute for Health and Clinical Excellence, for example, has traditionally only approved therapies which are valued at less than £30,000 per Quality Adjusted Life Year, effectively putting a dollar figure to the value of one year of life [NICE website]. However, in the US, the FDA may not make drug approval decisions based on cost, and payers are limited in this type of direct cost control by medical need and patient advocacy. Another potential mechanism for controlling costs has been to restrict use of specialty products, require prior authorization, restrict any off-label use (even when recommended by a specialist), increase the formulary tier on which a drug is available, and increase copayments and coinsurance for a drug. The latter trend especially has been accelerating in recent years. Medicare recently began requiring coinsurance for specialty products (i.e. Medicare part B pays typically pays only 80% of the cost of specialty products with multiple indications), and as the figure below clearly demonstrates (Figure 3), retail payers have followed suit, transferring more of the cost burden to patients, industry (through patient assistance programs), and charitable organizations and patient groups such as NORD. In fact, a Benefit Design Study by the Zitter Group in 2008 found that 70% of insurers raised copayment or coinsurance rates in the twelve months leading up to the study, and payers noted that they could typically transfer responsibility for more than \$350 per month to the patient without seeing members forgo medically necessary care¹⁹.

Figure 3: Cost burden shift toward consumer payments for specialty products

Source: InVentiv Advance Insights, Somerset, NJ



Where patients in these situations seek funding for drugs is yet another conflict area. Drug makers have fought back of late through a program where many manufacturers are providing coupons or vouchers which cover much of the out-of-pocket cost associated with a drug. For example, Enbrel and Humira are anti-TNF biologic treatments used to treat inflammation in autoimmune disorders such as rheumatoid arthritis and normally cost thousands of dollars each. The manufacturers (Amgen and Abbott respectively) issue cards which reduce patients' copayments to just \$5-\$10 per month, with the insurance company footing the rest of the cost and making very limited use of the drug company's own resources. This tactic contrasts strongly with the goal of patient assistance programs, in which the drugmaker instead foots the entire bill¹⁶. How long this tactic can continue is another matter entirely. Drug companies are using the coupon/voucher method to keep patients on branded drugs longer as well, and with major statins such as Lipitor going off-patent in 2011, the issue is in payers' direct line of sight, even irrespective of the specialty drug impact^A.

Foreign Approaches to Cost Issues

One direction to examine regarding how to potentially deal with the array of pricing, access, and reimbursement issues plaguing the specialty drug market is the way other governments have

tackled such problems. As several scholars have claimed (albeit with some caveats), “the US is the only major industrialized country without regulated prescription drug prices.”⁵² What is clear is that most other industrialized countries do indeed have controls in place to limit the system costs of healthcare in general and prescription drugs in particular. How have other nations managed to control these costs so effectively?

The European Union has a centralized orphan designation and approval process through COMP (Committee on Orphan Medicinal Products) and EMA (European Medicines Agency). This process is similar to the US in some ways (i.e. they share a designation request form), but different in others (i.e. market exclusivity can be revoked for drugs which are “sufficiently profitable”, although this provision has never actually been invoked). Orphan diseases are defined as those affecting fewer than five people in ten thousand, and orphan status confers 10-year market exclusivity, direct access to a centralized procedure for EU market authorization, a 50% fee reduction for regulatory procedures, and free scientific advice¹³. Although the laws have been successful in Europe as well (720 orphan designations leading to roughly 60 products by 2010) [European Medicines Agency Press Release, May 19, 2010], they have not seen quite the same level of impact as in the US, largely due to a lack of harmony between member state policies, although the EU is currently working to centralize even more of the process⁵². From a pricing and reimbursement perspective, however, member states differ widely in their approaches. In the UK, for example, as mentioned above, NICE may choose not to reimburse a drug if it deems the overall cost-benefit for a treatment to be minimal. Although NICE may be losing some of its power via a restructuring of the NHS, it still functions as a shield for payers to restrict coverage, as evidenced by its recent refusal to approve Roche’s drug, Avastin for use in metastatic breast cancer, following another rejection for use in colorectal cancer last year. As NICE chief executive Andrew Dillon remarked, “the evidence for the effectiveness of [Avastin] in prolonging survival wasn’t robust. Overall, [the drug] didn’t show enough of a demonstrable benefit for it to be considered a cost-effective use of National Health Service resources.”²⁹ As mentioned above, US law prohibits the FDA from making approval decisions based on cost, but the FDA in this case revoked Avastin’s use for breast cancer as well, citing efficacy concerns.

Other countries have similar rules in place to look at cost-effectiveness data, primarily affecting reimbursement decisions, not coverage. Many countries in the EU, for instance, reference prices in other member states in making decisions (i.e. Spain, France, Italy, etc). Several will look at

comparable treatments if they exist and try to determine whether a drug is truly “innovative”, and many will also try to limit coverage to only the most efficacious treatment in a class. Germany maintains a group to independently determine clinical benefit (called IQWiG), and has historically had more free pricing than the rest of the EU, but it recently restructured its system such that drug makers must now negotiate prices with individual sick funds. Canada warns drug makers that they must stay within “excessive” profit rates or risk limitation or prohibition on sales. Japan also implements an orphan program similar to the US, with 10 year market exclusivity, 6% tax credits and up to a 10% lower tax rate. However, Japan implements a sales tax of 1% on revenues above ¥100M until the subsidies earned during development have been repaid⁴⁸. These strategies have all worked to an extent to keep costs down. In 2008, prices for drugs in the EU were on average 40% lower than prices in the US, with Italy and Germany at 55% and 70% of US drug prices respectively⁵². As evidenced by the recently introduced legislation in Congress, this discrepancy rankles with US taxpayers. Thus the question we are left to consider is whether the US will ultimately consider adopting any form of negotiated prices for drugs in the future, and how would such a decision affect research, development, and marketing of specialty and orphan products going forward?

Chapter 3: Thesis Objective and Methodology

Thesis Objective

Several sets of professionals rely heavily on being able to predict revenues from orphan drugs. While the process of developing a drug is by definition extremely risky, both throughout the clinical phases and certainly when dealing with the various regulatory bodies in the US and abroad, it becomes even more difficult when considering the post-approval process which includes getting the drug priced, reimbursed, and adopted by physicians and patients. Financial analysts attempt to model these predictions in an effort to understand their effect on a company's stock and value, for which one blockbuster drug's performance can be immensely impactful. Drug companies similarly employ many individuals to help understand the post-approval process, in the hope of effectively predicting revenues, devoting adequate resources, allocating funds correctly, and understanding the competitive landscape and their brand image. The objective of this thesis is to try to understand which factors contribute to these forecasting models for orphan products, along with the sensitivities relevant to each, and to then examine potential factors which may be changing in the healthcare landscape, with the goal of understanding whether forecasting models as they currently stand in the US will remain accurate through a five year time horizon, based on the assessments of experts from across the various stakeholder perspectives in the healthcare space. Secondly, we will also attempt to examine the impact of the Orphan Drug Act through time, noting its successes and abuses and considering any additional challenges which experts anticipate experiencing in the short term future, with the goal of describing how stakeholders will need to adapt to any changing paradigms going forward.

Review of Existing Literature

An extensive review of existing literature was performed in order to begin to address the questions proposed and to better understand the historical context and current trends within the orphan industry, with the ultimate goal of forming the basis for discussions with industry and financial analysts as well as healthcare experts. This review encompassed scholarly articles from the fields of science, medicine, business, ethics, law, and health policy, as well as presentations and other publications put forth by regulatory bodies in the US and EU. Additionally, many articles in the press, journals, and other media were used as an indication of

current and relevant developments in the orphan product space. Company websites were used wherever possible to assess safety, efficacy, and sales data firsthand. The websites associated with the various regulatory bodies (such as fda.gov, e-rare.eu) also functioned as a good source to understand the challenges currently facing those bodies, along with recommendations for how to further the cause of drug research in general and orphan diseases in particular. Patient group sites such as NORD (www.rarediseases.org) and Orphanet (www.orpha.net) provided corroboration for statistics related to specific orphan diseases and drugs, and consulting reports were used whenever possible to help understand company strategies and trends in the orphan market.

Interview Guides

To assess our hypothesis that existing models fail to consider changes currently occurring in the healthcare system and to better understand the distinct elements of those changes, two interview guides were created, one suited for understanding baseline forecasting models, and the second for gathering the viewpoints of a wide array of healthcare experts. The forward-looking aspects of each interview guide are based primarily on data unearthed through the literature review process, and represent a fairly comprehensive view of the primary trends and developments impacting the orphan space. All questions were phrased in a fairly open way, representing the qualitative assessment each is meant to seek out. Additionally, each interviewee was asked one very open-ended question about major changes to the orphan space in the next five years, in an effort to allow the respondent to express his or her individual feelings about the most majorly impactful trends on the overall orphan drug industry and revenue forecasting process.

Forecasting Model Baseline Interview Guide:

1. Name/background/current position/experience with orphan products?
2. Can you describe the process of valuing a new orphan drug, including variables you consider, as well as their sensitivities?
3. What are the primary differences in US and EU/International policy which may impact the profitability of orphan products?
4. What are the key differences between forecasting orphan drugs and regular drugs?

5. Do you consider any potential upcoming legislative changes due to healthcare reform or potential new pricing limitations or pharmacoeconomic conditions when forecasting drug revenues?
6. How has the orphan market changed in the years since the law took effect (or since you began covering companies which make orphan drugs)?
7. If Gleevec or Cerezyme were launching today, what would be done differently and how might that change impact profitability?
8. What changes do you see in the orphan market in the next five years which may affect profitability? Are any of these factors taken into account in existing forecasting models?

Healthcare Expert Interview Guide:

1. Name/background/current position/experience with orphan products and legislation?
2. Has the orphan drug legislation been successful in your view? Why or why not?
3. Have there been abuses of the system in any way?^B
4. What is your opinion on blockbuster drugs which start in the orphan category and expand from there into multiple indications (orphan or otherwise) or which maintain very high pricing levels? i.e. Gleevec, Cerezyme, etc?
5. How do you think healthcare reform will impact orphan drug pricing? How will it impact orphan drug incentives overall?
6. Do you believe the orphan product space is currently undergoing an increased emphasis on pharmacoeconomics? How will this impact affect orphan drugs in the short/long term?
7. Will public outcry on drug prices and the determination to pursue cost containment in healthcare prompt a reexamination of the Orphan Drug Act? How might it change? Do you feel changes are warranted?
8. Do you think the FDA is employing a greater import on safety currently? Will the FDA amend the safety constraints for orphan products (whether more tight or lax)?
9. Do you believe big pharma will continue to pursue orphan indications? What impact will having more players in the orphan space have on the public view of orphan incentives?

10. Do you think there are any key differences in the market today over in the past (i.e. if Gleevec or Cerezyme were launching today, what would be done differently and how would that impact profitability)?
11. What other changes in the next five years do you see affecting the orphan market, from the perspective of pricing, reimbursement, regulation, incentives, or costs? How about longer term?

Selection of Interview Participants

Analyst interview participants were selected through several means. Financial analysts were selected by combing through the Investor Relations section of the websites of biotech and pharmaceutical companies which produce orphan products and subsequently tracking down contact information for several of these individuals and setting up a time to meet. This method met with moderate though limited success, as many of these analysts were too busy to arrange a meeting time in their schedule. Industry analysts on the forecasting side were recruited through professional network contacts as well as through contacts of my professors and thesis advisors, and these individuals were much more forthcoming in giving of their time and information to this thesis effort. While this imbalance certainly represents a bias toward industry forecasting mechanisms over those of the financial industry, our research and subsequent interviews revealed that this bias is in fact warranted, given the much more robust processes employed by industry in pursuit of accurate forecasts, as detailed below.

The healthcare expert pool ranged across a wide variety of stakeholder perspectives and experience levels, and given time constraints, an optimization process was undertaken to identify the most valuable candidates for interviews. These individuals were selected through a combination of contacts from my professional network, thesis advisors, thesis sponsors, HST professors, and leads drawn from preceding interviews. The result has been twenty-four interviews with experts from across the healthcare field, including industry professionals, commercial payers, government payers, providers, reimbursement experts, healthcare consultants, regulatory staff members / consultants, legislators, and patient advocacy professionals. These individuals represent a broad swath of the healthcare landscape, and their opinions, while clearly not fully representative of the overall healthcare field, are sufficiently informed to act as the basis of our limited pilot study and help answer our thesis questions.

It is worth emphasizing that the goal of these interviews was not to reach statistically significant conclusions, but rather to synthesize the initial impressions of stakeholders from across the healthcare landscape in light of the current market environment and to highlight any potential changes which may affect the validity of existing forecasting models used by both the pharmaceutical and financial industries.

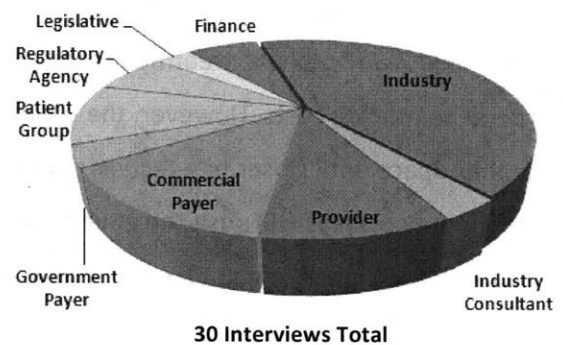
The selection of survey participants was intended to serve as an unbiased evaluation of the current state of thinking among those heavily involved in the healthcare space and to act as a framework for a future study with more significant resources. It is acknowledged that such a larger study may be necessary to justify both significant changes to existing models as well as any public policy implications, but we believe that the opinions elicited in this pilot study yield a reasonable perspective of what can be anticipated in the area of orphan drug development, and may further be extrapolated to help understand policy and pricing developments in the field as a whole.

The identities of all those interviewed is contained in an appendix to this document. However, their individual responses and quotes will remain anonymous and confidential for the purposes of this thesis.

Figure 4: Organizations represented by interview respondents

Represented Organizations	
• Biogen Idec	• CMS Massachusetts
• Leerink Swann	• FDA (Office of Orphan Products Development)
• Back Bay Life Science Advisors	• United Healthcare
• The Frankel Group	• Blue Cross Blue Shield MA
• Pfizer	• National Organization of Rare Diseases
• Enzyme	• AIDS Action
• Cambridge Neuroscience	• Congressman Barney Frank's Office
• Mass General Hospital	
• Beth Israel Deconess	

Figure 5: Breakdown of interview respondents by sector



Chapter 4: Interviews and Results

Summary of Analyst Interviews

Out of a total of six analyst interviews conducted, two were performed with financial analysts at two competing financial institutions in an effort to understand across the industry how the process of orphan drug forecasting is typically performed. The resulting strategy is fairly passive, in that they endeavor to receive guidance from pharmaceutical or biotech companies regarding pricing and adoption rates for a drug, relying on the sponsor company alone to perform the required sensitivity analysis and accurately discount the results. They can then estimate the number of anticipated patients and arrive at revenues based on an assumed price per patient per year, subject to the aforementioned adoption rates. A discount for competition is added as well, although this discount is clearly less relevant for most orphan products. Second to that, they will aim to corroborate this analysis using analogs if possible, although once again this process is often less feasible when assessing a drug in the orphan space. Additionally, analysts will discount the average sales price they are given by a factor of between 5% and 20%, to account for patient assistance programs and a lower hospital formulary price. On top of these discounts, they factor in some mandatory price cuts in the EU for government payers (often as much as 10%), and thus arrive at a revenue number. Regarding changes in the next five years, analysts interviewed believed that patient groups will become much better defined through registries and increasing connectedness among various populations and this in turn may lead payers to worry that with the advent of personalized medicine, ultimately every individual will have their own “orphan” treatment cocktail, with similarly high pricing causing an unsustainable rise in healthcare costs. However, the belief was that significant changes will not enter into the orphan space until closer to a *ten year* time horizon, by which point the realities of orphan treatment cocktails will push the government to interfere legislatively, and pharmacoeconomic data will additionally catch up with orphan drugs and force a justification for proposed pricing.

The four industry analysts interviewed presented a very different picture for the forecasting process, one which is much more robust and seems to feed into the information which financial analysts are given. As one industry consultant pointed out, “Wall Street just basically reports what they hear.” The primary variables considered in the forecasting process described by industry included the following:

- Understanding the drug's position in the treatment paradigm
- Competition, if it exists (including non-pharmaceutical approaches)
- Pipelines of other companies
- Epidemiology of the target condition
- Complementary or substitution-focused diagnostics which might amplify or decrease market share
- Proprietary position of the drug
- Manufacturing challenges or challenges to the manufacturing supply chain
- Marketing capabilities and effect on market share
- Route of administration
- Prices of anything which can be viewed as an analog
- Sales channel (PCP, specialist, etc) and expertise / ease of marketing to that channel
- Patient flow (from initial treatment to second line to treatment holiday, etc)
- Patient advocacy strength (affects pricing flexibility as well as regulatory predictions)
- Impact on life expectancy, quality of life, etc

These models also consider a particular drug's niche to better understand the expected adoption rate and resultant market share. This process asks questions such as: if a competing product exists, are there issues with diagnosis, safety, efficacy, or selectivity, in order to determine if a particular drug will grow the entire market, or merely snag some of a competitor's existing market share. In looking at the way orphan drug forecasting differs from regular drug forecasting, industry analysts pointed to the obvious dearth of competition in many cases, but also identified some more unique characteristics. In particular, they recognized public policy impact on speed of adoption due to high pricing as a concern which may contribute to the discount factor applied, as well as the difficulty associated with accurate predictions of both patient numbers and weight (for weight-based dosing). IMS, a primary source of drug data for industry, often does not cover smaller, orphan disease populations, and even physicians and specialists are often either inaccurate or simply misinformed in their estimates of total number of patients, forming selective biases based on geography, the condition of patients physically able to come see a physician, and the fact that affected populations may be shifting as well (i.e. the "baby boomer" generation reaching retirement age in the US beginning in 2011). Pricing is further tuned by testing proposed value with payers to understand formulary restrictions and

testing with physicians to understand prescription practices, especially if a copayment or coinsurance is likely to be involved. Revenues are then discounted for any increased regulatory risk associated with statistically lacking trials or surrogate endpoints used, to ultimately arrive at several bounded scenarios for pricing and adoption which lead to effective revenue estimates.

The process ex-US is similar, and most analysts do not break out country-specific numbers (unless the target population is geographically concentrated), but all amend pricing for government negotiations and incorporate a discount factor representing the potential for restriction based on QALY analysis in countries such as the UK. Additionally, convenience seems to garner a much lower pricing premium in EU countries focused on clinical value, so pricing theory is instead focused on benefits of reduced hospitalizations, complications, and mortality.

What these detailed models do not seem to include, however, is a map of additional indications which might be pursued (as this can present serious regulatory issues) or significant off-label use which may greatly bolster sales (one analyst noted that Provigil, Cephalon's analeptic drug, has wide-spread off-label use, accounting for an estimated 80% of its \$1.1Bn in 2010 sales), as well as discounting associated with scenarios such as a change to US law to emphasize pharmacoeconomics or changes implemented by specific payers which amend the rules for copayments and formulary restrictions in the years beyond launch. Changes to stipulations of the Orphan Drug Act could also redefine the orphan space and change the patent and marketing protection for a product as discussed above. Although it is unrealistic to attempt to predict the future in a revenue model, scenarios demonstrating the lower bound of revenue projections could reasonably be expected to include any impending changes to these very significant market factors as a discount factor to overall revenues, allowing the company to create contingency plans should these changes, in fact, occur.

When asked if they believed that any similar changes may be imminent in the short term (up to five years out), analysts expressed several perspectives. One respondent predicted that pricing pressures would continue to mount across the medical landscape, and with those rising pressures will come public outcry over drug prices, but ultimately no action on orphan medications, as patients and patient advocacy groups will continue to clamor for next-generation drugs. Others similarly indicated that although public outcry will continue, people will pay for value when they see it, and while payers may clamp down on drugs which present very limited value, it will be *at least 10 years* before this process catches up to orphan products.

Government payers may increase some restrictions, and EU reimbursement scenarios may in fact change significantly, as France ponders allowing a maximum of €50,000 per patient per year and other governments consider standardizing risk-sharing deals, including a revenue claw-back above a certain threshold, all within the next five years, but the probability of these types of explicit price controls making it back to the US in a significant way were thought to be very slim. Finally, healthcare reform's impact on the rare disease space was thought to be negligible as well, as assisting patients with access to drugs (through removal of the lifetime cap on insurance payments, etc) was thought to be extraneous in that patients would never be denied a life-critical treatment, due to the negative public relations outcry such an event would engender, and as such, patient assistance programs already functioned to provide this same access.

Thus, the overall sentiments from industry and financial analysts are that the broad array of factors which currently contribute to drug forecasting, as well as those factors which are unique to orphan drugs, do not currently account for impending changes to legislative, pharmacoeconomic, or other factors. They contend further that the models are accurate as they currently stand in that they reflect all current factors relevant to post-approval performance of a drug, and that any changes to the legislative or reimbursement picture such as those discussed above were not relevant for inclusion in their respective models given the short time frame being discussed and the inertia in enacting modifications related to the treatment of orphan diseases.

Summary of Expert Interviews

Of the 24 expert interviews conducted, 3 claimed to have limited knowledge of the orphan space and were subsequently excluded from the interview process, leaving 21 qualitative interviews from which to draw results, or 87.5% of the total.

Within those who were deemed sufficiently knowledgeable in the orphan space, the list includes nine members from drug companies, servicing a variety of different roles, along with four commercial payers, two regulatory agents, one legislative representative, three administrative members of patient groups, one government payer, and three care providers, thus creating a fairly representative sample for our pilot study, drawn from across the healthcare landscape.

In order to clearly define the results of the expert interviews, we will lay out the conclusions which will help answer the thesis questions, and subsequently discuss all feedback on a question-by-question basis from across the full range of experts.

Expert Interview Conclusions

Although individually, many of the experts interviewed presented mixed opinions about the future of changes to legislative and pharmacoeconomic elements affecting the orphan drug market, the overarching direction of their thought processes were largely parallel with only one or two dissensions (discussed below).

The reality which seems likely to emerge in the next five years is fundamentally similar to the way things have been done in the past, with more significant changes emerging only over the longer term. Highly innovative and effective drugs will continue to command the price premiums which they have in the past, but those of more marginal efficacy may increasingly need to validate their pricing and approval with solid pharmacoeconomic data. Regulatory conditions for orphan indications will gradually become clearer and may also begin to officially allow more lenient trials for some orphan products, including the use of historic or dose curve controls as well as surrogate endpoints with follow-on post-approval studies to help determine efficacy. Payers, led by those in Washington, will continue to impose restrictions on drug use, attempt to negotiate as best they can with manufacturers, lead the evolution of risk-sharing deals in the US, and ultimately pass on a higher burden of the cost to consumers, all while constructing ever more complex methods of tracking outcomes to better determine clinical value on their own. However, due to the public relations issues inherent in restricting orphan drug coverage, the FDA will function as more of a gatekeeper on keeping coverage away from less effective orphan drugs through its approvals process. Large companies will continue to try to adapt to the orphan market paradigm with mixed success, and advances in diagnostics will increasingly impact orphan development and improve outcome measurements. Several new technologies on the horizon may, in fact, dramatically shift the fundamental mechanisms affecting the orphan market. Both personalized medicine and gene / stem cell therapies have the potential to create a mass of orphan indications, which could put so much pressure on costs as to force a reformation of legislation and / or adjustment of payment schemes. Conversely, this same change resulting from an increase in “personalized treatment cocktails” might in fact

result in a redefinition of orphan designations along molecular lines, causing several oncology indications which today are considered orphans to no longer qualify and thus actually *shrinking* the pool of orphan indications. Barring a significant paradigm shift, however, the predominant feeling among most stakeholders is that although orphan indications may no longer be considered “under the radar” for payers, the options for addressing the cost and reimbursement issues they present are limited in the short term and will ultimately be overlooked in favor of lower hanging fruit. When looking at a slightly longer time horizon, several additional changes may be likely to occur, potentially including government caps on expensive medications, payers driving PE data requirements to justify pricing, and more effectively negotiated pricing (similar to what is commonly done today in the EU).

Discussion of Specific Interview Questions

Has the orphan drug legislation been successful in your view? Why or why not?

In this case, almost every expert interviewed agreed with the literature in stating that the legislation was successful. However, there remained a range among the responses. While Dr. Tim Cote declared that “there is no question that the Orphan Drug Act is without a doubt the single most successful piece of legislation that has ever been passed in human experience,” others were less enthusiastic. What is clear is that the law has done its job to encourage development for many rare diseases whose patients would otherwise likely be without treatment today and that in doing so it effectively launched and built the biotech industry into its current form. Despite these successes, however, some experts also noted that we currently only have treatments for 200 out of the roughly 7000 rare diseases in existence, and that the incentives of the Orphan Drug Act only go so far in encouraging for-profit corporations to pursue treatments for incredibly rare indications. Others similarly noted that the provisions of the ODA cater more to smaller companies than large ones for a variety of reasons. First, the private nature of many smaller companies means that they can more legitimately pursue smaller markets with the hopes of more modest profits without fearing public scrutiny. Additionally, grants issued by the FDA’s Office of Orphan Product Development as well as the waived user fee for the NDA can make a serious difference to a cash-strapped small business. Finally, the smaller sales force required to market orphan drugs combined with the explicit marketing exclusivity

clause conveyed with orphan status allows smaller firms to raise capital more easily than for traditional indications.

Have there been abuses of the system in any way?

The only abuse of the system which came up repeatedly (mostly from patient advocacy groups) relates to generic drugs which have been subsequently designated for an orphan indication (such as Colcrys, Makena, and Acthar Gel). While the company inevitably must perform requisite clinical trials and gain FDA approval, there is little true innovation going on to justify the prodigious price increases which may then have the effect of limiting access to the drug once approved. Industry counters this by contending that more physicians will use the drug for its indication once it has a label, FDA approval, and proper dosing regimens for the orphan indication, thereby *increasing* access for patients. Further, these companies will often justify the price points based on alternative treatment costs. However, many experts argue that this is fundamentally a marketing innovation and not a research advance, and as such is unfairly taking advantage of the orphan drug status it was granted. One expert also noted that even assuming most of the cost of these high-priced drugs is pumped back into R&D for future products / indications, patients often feel that they are shouldering an unfair burden of treatment for someone else's disease. That said, most respondents felt that the Act was serving primarily as intended and that companies were for the most part trying to make use of its incentives to do good.

What is your opinion on blockbuster drugs which start in the orphan category and expand from there through multiple indications (orphan or otherwise) or very high pricing? i.e. Gleevec, Cerezyme, etc?

Most experts who responded to this question claimed that it was unfortunate in some ways for patients, but ultimately a drug which pursues multiple indications or generally treats a disease very successfully deserves to earn a significant premium, and this scenario is thus both warranted and sustainable. As one provider explained, "[Distress over an orphan drug's expansion to other indications] is like setting up a homeless shelter and one of the members goes on to become a billionaire." At times it is not even multiple indications which increase a drug's target population, but simply the fact that it turns a previously fatal disease into a manageable illness, thereby using the success of the treatment to increase the patient pool, as

many enzyme replacement therapies have done. Several experts claimed that they would certainly support a claw-back clause to recover taxpayer subsidies for revenues above a certain threshold or in response to expansion to multiple indications, but they quickly admitted that since the market will bear the cost of these successful medications and recognize their value, there is little incentive to change.

How do you think healthcare reform will impact orphan drug pricing? How will it impact orphan drug incentives overall?

The impact of health reform on orphan drugs seems to depend largely on perspective. The law itself only contains a few clauses which might impact orphans, namely:

- Removal of a lifetime cap on insurance payments
- Removal of prior condition exclusions
- Allowance for young adults to remain on parents' insurance policies until age 26
- Creation of an Independent Payment Advisory Board (if given real power to target prices, which remains to be seen)
- Implementation of an excise tax based on market share for brand name sales to Medicare / Medicaid / DOD / VA; orphan drugs are excluded *unless* approved for broader indications
- Establishment of Patient Centered Outcomes Research Institute, funded with \$650M through 2019 to evaluate efficacy based on outcomes (orphan drugs are excluded for the moment)

Experts here divided largely along stakeholder lines. Industry experts claimed that although the first three elements should in theory help increase patient access to drugs, in practice most payers already account for that, and the plethora of industry-sponsored patient assistance programs means that there are very few cases where patients would not be able to get access to a medically necessary treatment. From a financial perspective, they pointed out that the law does very little to change pricing practices for any drugs at all, and certainly for fringe products such as orphans, "healthcare reform was the only vector to change the way drugs are priced, and we missed that." Only payers seemed to think that the law's indication that costs will get squeezed may have broader ramifications in forcing everyone to control pricing, even for rare and effective products such as many orphan drugs, "in general, all healthcare players will have to find out how to make do with less."

Do you believe the orphan products space is currently undergoing an increased emphasis on pharmacoeconomics? How will this impact affect orphan drugs in the short/long term?

One might expect this to be a controversial issue given all the emphasis placed on pharmacoeconomics in ex-US countries as discussed above. Indeed, some larger plans with clinical pharmacists on staff are already analyzing disease progression and outcomes data for non-orphan indications. However, most experts agreed that while PE is certainly helpful in demonstrating the value of a product and that it may in the next five years play a more central role in the pricing and access determination of other, traditional drugs, for orphans its use will remain marginal. Several respondents pointed out that while it sounds terrible to say, from a strict pharmacoeconomic point of view, the most “valuable” course of action for those patients with a condition which is expensive to treat is to let them die. Thus, PE studies are by definition often flawed in the case of orphans and so are rarely used in their simplest sense of demonstrating a positive cost-benefit; and QALY analysis, everyone agreed, is unlikely to migrate to the US anytime soon, “price restriction similar to the EU is the perfectly rational thing to do, but I can imagine the reaction from the tea party and others.” Furthermore, orphan drugs are often restricted to prescriptions from specialists, making payers more comfortable that they are only being used when necessary. Additionally, there are significant public relations concerns when considering denying coverage for an indication with unmet medical need. As one expert dramatically pointed out, “[payer medical directors] never want to go in front of a camera and say they can’t help little Susie because they don’t want to pay for it.” Other payers pointed out further that although many drugmakers are now designing trials with the goal of generating PE data, few payers trust this data enough to base pricing decisions on it; instead some payers are attempting to create their own outcomes tracking databases, although many expressed doubts about the usefulness of these databases as well, being that they are targeted toward tracking patient outcomes and not specifically drug effectiveness.

Will public outcry on drug prices and the determination to pursue cost containment in healthcare prompt a reexamination of the Orphan Drug Act? How might it change? Do you feel changes are warranted?

Responses to this question were very clear and differed only mildly across stakeholders. While published articles will occasionally spark public outcry and even Congressional outrage, the bottom line is that industry, patient advocacy groups, and physicians concerned primarily with

having more options available for treating patients actually do not want the law to be reevaluated in any way in the short term. There are still over 6500 diseases for which no treatment is yet available and patient groups are concerned that any tinkering will cause a decline in the research aimed at treating those conditions. Indeed, if the proposed amendments to the law in the early 1990s caused a significant dip in orphan designation requests as discussed above, there is certainly reason to believe that an angry Congress reworking the law would have serious adverse effects on industry's willingness to participate in orphan disease research. In fact, there is pressure from several fronts to *increase* the incentives offered, whether through easing regulatory burdens further or by encouraging pharma to open candidate libraries to high throughput screening by the NIH. Most payers seemed resigned to the law remaining unchanged (although they certainly were interested in change), but one highlighted the trending increase in copayments and coinsurance as a way to keep drugmakers honest. They reasoned that with consumers sharing a larger burden of the cost (whether the end result of this practice hits the consumer's pocket is still unclear) there will be a drive for transparency in pricing which will not allow egregious price increases to go unnoticed, initiating a "day of reckoning" for actual drug value.

Do you think the FDA is employing a greater import on safety currently? Will the FDA amend the safety constraints for orphan products (whether more tight or lax)?

Only a few experts felt they were in a position to comment on this point, but the overarching feeling seemed to be that standards for acceptance of orphan trials were still not very clear, and that the agency must do a better job of clarifying the regulatory pathway for orphan products. In that vein, the FDA established a "Rare Disease" unit within the Office of New Drugs in 2010 to help facilitate approval for orphan treatments. However, for the time being, there is still a significant gap between looking at what the FDA has accepted historically as evidence for approval and being certain of what will be considered sufficient in the future, especially as traditional drugs face increasingly tough standards for obtaining approval. The FDA would generally prefer to see placebo-controlled trials with enough patients to demonstrate statistical significance and a valid safety profile. While the safety profile issue may be relaxed in orphan indications, running a placebo-controlled trial when another treatment exists is often unethical, and finding enough patients to demonstrate significance can be time consuming or even impossible. Patient groups and providers align closely with industry on this point, as their

primary goals are to enable more treatments for more diseases more quickly. That said, since orphans typically have high mortality rates and a large unmet need, it has historically been fairly easy to convince the FDA of clinical benefit. Many ERT studies have sufficed with using either historic or dose-curve controls and no placebo. Surrogate endpoints are not currently commonly used, but have been allowed in specific circumstances (Avastin, for example, was approved based on a surrogate endpoint). Yet respondents suggested that surrogate endpoints combined with post-approval studies of outcomes to determine efficacy may be crucial policy in approving orphan products in the future in order to compensate for the small number of patients and long time horizons or ethical considerations that using an endpoint of mortality would suggest. Unfortunately, due to the difficulty of running trials once a drug has been approved, the FDA often does not believe it will ever be privy to the post-approval trial results and so is still reluctant to create a standard guidance based on this regulatory pathway.

Do you believe big pharma will continue to pursue orphan indications? What impact will having more players in the orphan space have on the public view of orphan incentives?

There is little question that large pharmaceutical companies have made it clear externally that they would like to take a bigger role in the rare disease space. What is not entirely clear, however, is how they intend to pursue this goal or whether they are in fact adequately prepared to succeed in this market. For all the media hype, several industry insiders pointed out skeptically that most pharma companies have not created new units to specifically perform R&D on new orphan drug candidates. Rather, they have primarily been engaged in a strategy to scour the late-stage pipelines of smaller companies and attempt to pick off the winners. This is not so much an effective way to help create innovation for unmet medical need as it is a way to restock a depleted pipeline. Further, many experts feel that with large sales forces dominating the pharma landscape, the emphasis in rare diseases on individual patients means that orphans will never succeed as a large part of the business model. As one prominent patient advocacy group leader unequivocally stated, “big companies don’t understand the business model which is very unique and very different.” Indeed, several smaller companies have sprung up to try to perform patient services for big pharma companies unprepared or unwilling to do this work for themselves (one example is Centric Health Resources). Additionally, payers may expect to see lower prices from companies with deep pockets and pricing practices may therefore be volatile from a public relations perspective (although somewhat offset by the positive PR from

addressing an unmet need). Finally, often corporate integrity agreements at large pharma companies prevent them from engaging directly with patients in the way that biotech companies do as part of standard business practices. Thus, the overall perspective was that most stakeholders are unimpressed with big pharma's claim of jumping into orphan drugs (although it is a bit more difficult to argue with Sanofi-Aventis' purchase of Genzyme for over \$20Bn), and most do not believe it is a sustainable new market for them as currently structured. That said, payers were obviously not thrilled with the prospect, but believed that unless the number of approved orphan products jumped 10-fold in the next few years, they would keep covering drugs in the orphan space even coming from larger companies, as the negative PR earned from denying coverage remains a poor tradeoff. Additionally, the consensus was that for big pharma to get into orphan diseases in a truly meaningful way would require spinning off a separate company to perform real R&D on prospective candidates with more of a biotech business model attached to it, encompassing intimate patient support and appropriate marketing services.

Do you think there are any key differences in the market today over in the past (i.e. if Gleevec or Cerezyme were launching today, what would be done differently and how might that impact profitability)?

Again emphasizing that in the short-term the orphan industry will largely remain the same, experts asserted that in cases of clear value such as Gleevec or ERTs such as Cerezyme, high prices would be expected and tolerated. Cerezyme has demonstrated the ability for a drug to increase its patient population by virtue of creating a manageable illness out of a fatal disease, but while it is possible that regulators and payers will start looking at the potential for new indications when considering orphan drugs, on the whole such a development is unlikely. What *does* tend to rile payers are when pills are priced like biologics in treating the same illness (since the margins are significantly higher), as well as any effort to significantly raise prices after launch or to introduce different prices for a change in dose. The latter was attempted recently by Genentech, as it was discovered that Lucentis, a treatment for wet macular degeneration, was very similar to Avastin, but required a much smaller dose (thereby eliciting a much lower price). In order to keep prices up, Genentech claimed that they were in fact different molecules, but the NIH elected to undertake a trial to show that they are functionally equivalent, allowing physicians to simply use a small amount of Avastin to treat patients with WMD. Additionally,

when looking at orphan drugs which are slightly less effective than blockbusters such as Gleevec or Cerezyme (such as many of the newer cancer medications) as well as ultra-orphan indications, there may in fact be different market factors in play nowadays, as it is harder for small firms to find funding for such drugs, and the regulatory pathway as discussed above is extremely murky. One element which may be changing (again, primarily for less effective treatments or drugs targeting much smaller patient populations) is the incidence of risk sharing deals where the pharmaceutical maker agrees to shoulder some of the risk for treatment efficacy. This initiative seems to be slowly gaining steam, especially in the EU, and many experts thought this was something which may take hold back in the US as well.

What other changes in the next five years do you see affecting the orphan market, from the perspective of pricing, reimbursement, regulation, incentives, or costs? How about longer term?

Many important trends were identified as likely to either increase or continue, but none would qualify as a large-scale change in orphan market factors which might significantly impact current forecasting models, although it may potentially be more difficult to get approval of drugs which are only marginally innovative or efficacious. The *short-term* changes highlighted, with stakeholder identification, were:

- Big pharma may become more conservative and lose interest in orphan indications (provider / industry)
- FDA regulatory process will become clearer (industry / patient group)
- Share of costs shouldered by patients will continue to increase, even up to 20% (payer / patient group)
- Payers may continue to impose restrictions on orphan drug access through formulary tiers, etc (patient group)
- FDA will function as the primary gatekeeper for orphan drug coverage, as once approved, most drugs will continue to receive coverage (industry)
- Rare disease research (especially for ultra-rare diseases) will become more heavily dependent on charities / patient groups over industry (provider)
- Better risk pooling for people with chronic illnesses, potentially even government stepping in to pay for those patients (payer)
- More harmonization with international designation process, no major regulatory changes (regulatory)

- Biologics slowly replaced by orals, but this will not lower prices much for orphans (industry)
- Marginally efficacious drugs will have a harder time commanding the same reimbursement rates as more innovative ones (government payer / industry)
- More price negotiations with manufacturers by both government and commercial payers (government payer / industry)
- Government payers, as they become stressed to deal with costs, will require “coverage with evidence” (a form of forced outcomes research) and will use the national coverage process to help deal with costs (government payer / industry)
- As physicians affiliate more with managed care and hospitals and band together, they will increasingly have power to negotiate with manufacturers over prices as well (industry)
- Payers will begin tracking outcomes more effectively in an effort to generate their own efficacy data (industry)
- Diagnostics will play an increasingly large role in helping drugmakers to demonstrate the value and effectiveness of their products (industry)
- With growing pressure for access to new treatments, surrogate endpoints combined with post-approval efficacy studies will become more accepted in the orphan space (industry)
- More of the same (industry / payer / patient group / regulatory)

Several stakeholders did mention that looking at a slightly longer time horizon, several additional changes may be likely to occur, potentially including government caps on expensive medications, payers driving PE data requirements to justify pricing, and more negotiated pricing (similar to what is commonly done in the EU). Additionally, as mentioned above, several technological developments such as the emergence of gene and stem cell therapies, personalized medicine, and molecular diagnostics may necessitate a reworking of the orphan drug legislation to more narrowly define products which are eligible for orphan incentives.

It is also important to note that there were two dissensions from among the responders, one of whom articulated that due to mounting budget constraints, pricing is coming under pressure in both the EU and the US, with the implication that it is very possible that in the next five years data will be required to show the value of treatment in both geographies and orphan pricing will come back to earth as more payers recognize their growing overall burden. The other dissenter was more moderate, and made it clear that we are currently in a state of flux, “we are witnessing a culmination of two very different political philosophies or ideologies around this, and the politics are not necessarily functioning at the moment to work it out, but we are seeing unprecedented pressures toward cost containment; and at the same time we are looking at a

fear of rationing, sometimes from the same people.” That said, “I do know that the days of drug companies and specialists writing blank checks on these drugs is over—there will be much more scrutiny on the value of these drugs and what does clinical value mean.” Most experts, however, did not agree, as one payer resignedly pointed out, “a \$1M pill is likely to launch in the next two years and our hands are tied in US.”

Thus, the reality which seems likely to emerge in the next five years is something of a compromise. Highly innovative and effective drugs will continue to command the price premiums which they have in the past, but those of more marginal efficacy will need to validate their pricing and approval with solid PE data. Regulatory conditions for orphan indications will gradually become clearer (and possibly more lenient), and payers, led by those in Washington, will continue to impose restrictions on drug use, attempt to negotiate as best they can with manufacturers, evolve further risk-sharing deals, and ultimately pass on a higher burden of the cost to consumers, all while constructing ever more complex methods of tracking outcomes to better determine clinical value on their own. Still, due to public relations issues with restricting orphan drug coverage, the FDA will function as more of a gatekeeper on keeping coverage away from less effective orphan drugs through its approvals process. New technologies, including gene and stem cell therapies, personalized medicine, and diagnostics will increasingly impact orphan definitions and development, and large companies will continue to try to adapt to the orphan market paradigm with mixed success.

Chapter 5: Discussion

Through this limited pilot study, we examined the potential of several trends within the prescription drug landscape to significantly alter the value proposition of orphan drugs in the short term future. Although the net effects of these changes would be wide-ranging, we elected to use forecasting models employed by the finance and pharmaceutical industries as a tangible example of those directly impacted by our results. As such, we interviewed analysts from both industries to obtain a baseline from which to assess changes in the short-term future of the orphan drug space. A five year time frame was selected as the most reasonable in that it balances the slow speed of enacting meaningful changes (whether legislative or otherwise) with the ability of industry stakeholders to make educated predictions about emerging trends and paradigm shifts.

We subsequently focused on attaining a broad picture of the concerns of stakeholders from a wide-range of healthcare functions, including various functions within industry, patient groups, providers, legislators, regulators, and industry consultants, and we deliberately asked open-ended questions in the hope of arriving at meaningful qualitative conclusions. In order to form the basis for the interview questions and to have a strong background from which to discuss interviewee opinions, an extensive literature review was conducted to better understand several influential elements: the history of orphan drug legislation both in the US and elsewhere, public and industry concerns over current pricing, access, and reimbursement mechanisms, specific company profiles, and current trends as reflected in journal articles and the media over recent months.

Our hypothesis that existing forecasting models will fail given impending changes to influential market factors in the orphan drug space was not supported, as it would appear that at least over such a short time horizon, most variables currently employed in orphan drug models will continue to be relevant as before. However, two important factors came to light which qualify this result. First, when considering a slightly longer time horizon many experts did, in fact, expect significant changes to the orphan drug reimbursement paradigm, whether due to legislative, regulatory, or technological shifts, as pressures on costs driven by payers, patients, and physicians continue to mount. Furthermore, drugs which display marginal efficacy (and the definitions for marginal efficacy will likely become more clear as well) may indeed face the need

to justify their pricing in the next five years, and may in fact be subject to significant restrictions and lower prices than their wildly innovative and effective orphan counterparts. This difference should indeed be reflected in forecasting models, though to say that they will *fail* if used in their current state based on this subset of drugs is unfair. This prospective change is also subject to the caveat that so long as patients clamor eagerly for the newest medications, and so long as political figures follow their lead, even less-effective drugs may yet continue to command high prices despite the outrage this may generate, as public relations issues continue to dominate more rational payer policies, leaving only CMS to lead the way in addressing high prices.

Implications

While the hypothesis was not supported, our results have significant implications for analysts as well as those either currently operating in or preparing to enter the orphan drug market. Understanding stakeholder biases and motivations can significantly help mitigate the effects of unexpected change, and as several technologies have the potential to capriciously amend the definition and treatment of orphan drugs, it is imperative that companies active in this space keep a close eye on the progression of those fields. Long range planning guidance should consider the changes likely to take place after the five year mark as well, and, as we have shown, such changes have the potential to be very significant in their own right.

The implications from these results also resonate on an individual level for stakeholders. Regulators should understand the confusion around the orphan drug pathway and seek to clarify details around surrogate endpoints and studies with non-placebo controls. Payers should continue to be mindful of the threat orphan drugs present to their cost structure and must become leaders of innovation in managing these products, whether that includes designing and implementing research-oriented databases to understand drug efficacy, working to implement new risk-sharing deals, or pressuring government payers to take the politically difficult lead on tackling drug prices. Patient groups and physicians must be aware of the funding shortage likely evolving for ultra-orphan indications, and need to temper their enthusiasm for new treatments with an understanding of the benefits of keeping healthcare costs down. If forgoing approval of a therapy which extends life for one month in a cancer patient means that there will be funds for creating a cure for a disease affecting 1000 people worldwide, that ethical conundrum will likely be partially decided indirectly by their efforts. Similarly, pressing for less-effective new

treatments to be reimbursed means that a growing share of drug payments will continue to be borne by patients, which may ultimately lead to decreased access on a much broader scale. Legislators, by virtue of their political agenda, will always play to public sympathies, and while the Orphan Drug Act may be largely safe from tampering, transparency has its benefits as well, and pushing for cost containment in intelligent ways which the public can rally behind could provide a change the field desperately needs. Pharmaceutical and biotech companies will need to adjust in the coming years to the new reality that less effective drugs will likely be subject to lower prices and higher data requirements, whether this reality is enforced by payers or by the FDA. While this certainly adds some risk to all drug development and even greater risk to *orphan* drug development, it remains an area where drugmakers can take the lead as well in creating innovative solutions. Improvement of the science of generating standardized pharmacoeconomic data through trials will allow payers to trust more in the resultant care offered to the patient. Risk-sharing deals, which are already growing in popularity in the EU, are likewise a very effective way to convince a doubtful public and payer community that a drug is truly delivering the value it commands as payment.

Limitations

The selection of both analysts and expert interviewees was intended to provide a wide view of ongoing trends in the orphan drug space and to enable this study to serve as a roadmap for future research, not necessarily to reach statistically significant conclusions. Time constraints and the difficulty of contacting some individuals limited the experience level of several of the respondents, and our attempt to reach a wider array of experts left fewer individuals representing each specific stakeholder position. Additionally, the diversity of experts contacted represents a large segment of the healthcare landscape, but is by no means a fully representative sampling. For example, our legislative contact was limited to one Congressional staffer, and several attempts to contact Massachusetts state public health institutions were rebuffed. Similarly, we could have extended interviews to those running patient assistance programs, hospital formulary managers, pharmacy benefit managers, etc.

Another limitation is that our pilot study is very focused on those in the Massachusetts area, and this geographic bias can potentially have an impact on our results as well. Various payers across the nation are endeavoring to deal with cost issues in different and creative ways, and our focus

on the Northeast has limited our exposure to those ideas. Several individuals interviewed neglected to comment on one or more of the questions, for fear of being quoted out of context on areas which were not directly related to their official capacity, or for fear of having their ideas assigned back to their respective institutions. Due to the methods for recruiting individuals for interviews, there is a possibility of selection bias as well, as apart from those within industry, many of the experts have direct academic ties, which might potentially cause them to share a unified view of emerging trends in the drug industry.

There is clear variability among the experts interviewed relating to their familiarity with either orphan drug legislation or specific trends within the healthcare landscape. Many refused to answer questions with whose subject they were only passingly familiar, and still others tempered their claims by stating unequivocally that they were only speculating on specific issues. In all cases, these remarks have been lent lesser weight in our results, but they still represent one limitation of presenting a wide-ranging questionnaire uniformly to a diverse group of people.

Future Research

Our discussion with stakeholders from across the healthcare landscape has significant implications for future research and may serve as a roadmap for follow-up studies with greater resources. While many of the projected changes do not seem poised to affect the orphan drug market in the short term, longer term implications clearly have the potential to significantly alter forecasting and revenues in the orphan drug space.

Repeating this study five years from now, for example, would be a fascinating commentary on the pace of change in the healthcare industry, and would yield a better understanding of what factors, if any, have the capability to quantifiably impact orphan drug pricing and reimbursement in a rapid way. The study could further be extended to include many additional stakeholders in the healthcare space to attain an even broader view of prospective changes, and could also be amended to provide a retrospective analysis of changes occurring between today and such a future date, eliciting an understanding of common biases shared by those involved in the healthcare space.

Further studies may also choose to assess a larger array of impacted areas; for example, understanding how employment opportunities may change based on paradigm shifts in orphan drugs, or assessing where the balance of power may be found among different stakeholders at various times in history and how such a power shift might further impact commercial and public strategies going forward. Our results could also serve as a basis for more quantitative work, examining actual drug revenues as compared to analyst predictions over time to understand which market factor changes led most frequently to inaccuracies, with the goal once again to devise strategies which may be undertaken to effectively mitigate these situations.

Future work may also be conducted by specific stakeholders with potentially interesting results, as a study of a similar nature undertaken by the FDA, for example, might motivate a reassessment of some of the uncertain regulatory issues surrounding orphan drug policy or may lead to more creative solutions to some of the problems encountered based on the specific influence available to those performing the study.

Chapter 6: Additional Challenges

The results obtained from the literature review as well as the stakeholder interviews highlight the very real challenges involved in the process of creating pricing, reimbursement, and access standards for orphan products which allow for a fair sharing of value among all involved parties. These challenges are greatly exacerbated by the fact that while making people better is simply a business to some, it is a matter of life and death to others, and emotions tend to rule the day. Thus, the sensitivity of applying any form of economic analysis to the ethical and highly personal issues which permeate the orphan product space must be carefully considered from multiple distinct perspectives in order to effectively view the entire picture. That said, while drug revenue models may not be changing dramatically in the next five years, it is worth examining in detail some of the more impactful trends which may be emerging to attempt to devise effective and progressive mitigation strategies for dealing with them.

Generics Marketed as Orphan Products

One of the trends which has never failed to elicit a strong and emotional response from payers, politicians, patient groups, and the general public is the practice discussed above wherein drugmakers run trials and receive approval for an orphan indication based on a molecule which is already available as a generic, and which may already even be fairly widely used for the same indication. As one payer succinctly put it, “rehabilitated drugs drive up healthcare costs under the guise of cost-effectiveness.” In a recent article in the *New England Journal of Medicine*, several physicians argue the case against Colchicine (brand name Colcrys), a drug approved for acute treatment of gouty arthritis, whose ancestral plant was already being used to treat gout as early as 3000 years ago, and whose tablet form was widely available as a generic in the US since the 19th century. The manufacturer, URL Pharma, further applied for and received seven year exclusivity for the orphan indication of familial Mediterranean fever based on a review of previously collected data and pharmacokinetic trials. As the price subsequently jumped over 50x, the authors argue that patient access was thereby restricted, and funds were diverted from other worthwhile healthcare causes to pay for the newly branded medication. This case therefore reveals a flaw in orphan drug incentives which negatively impacts the overall healthcare market²³. While it is difficult to argue with the case that some rebranded generics represent a failure of orphan incentives, drawing a clear line is not nearly as simple as

disallowing the application of incentives to non-innovative products. How does one determine the actual added value of FDA approval and correct dosing? How many new trials need to be run to justify a given price increase by a manufacturer? With arguments in each direction, can anyone actually quantify the change (positive or negative) in patient access to a drug once it attains FDA approval? These questions must be answered in an evidence-based approach before drastic action may safely be taken. Were the NIH to sponsor trials for drugs which are known to be effective for a given condition in order to preempt a drug company doing so for profit, everyone might benefit at a fraction of the cost, yet until this concept catches on, drugs such as Colcrys and Makena will continue to rile the media and give the orphan drug system a bad name.

Government Recommendations

Between 2008 and 2010 both the US and EU commissioned reports for recommendations in helping to advance the cause of rare diseases. The US report, which was jointly conducted by the FDA, the NIH, and the Institute of Medicine, examined the challenges in attracting public and commercial funding for R&D, obtaining sufficient numbers of research participants, designing sound clinical trials, and truly assessing safety and efficacy prior to marketing approval²⁰. A similar study was put out by the European Commission in 2008, and the results of this second study present a good indication of how the EU is encouraging stakeholders to tackle several of the major challenges facing the orphan product space. First, the report emphasizes the importance of establishing early dialogue between companies and pricing / reimbursement authorities to discuss clinical data needed for later clinical value assessments, thus providing the company with more certainty around the process and the authorities with more trust in the trial results. Second, the report requests greater knowledge exchange between member states on the added clinical value of specific drugs. Third, it encourages initial uptake through conditional pricing and reimbursement decisions, thus allowing faster access to patients while controlling utilization, budgets, review timing, and further studies. Finally, the report encourages building EU-level expertise in rare diseases, creating EU-wide patient registries and networks of centers of expertise, and assistance with supply issues as well as post-approval studies⁸. These suggestions are equally applicable to the US in combination with the EU, as encouraging better use of global patient registries, more open dialogue with regulators and reimbursement agencies, knowledge exchange (both clinically and from a value perspective), and more wide-

spread implementation of risk-sharing strategies are concepts that are universally necessary and would benefit the widest spectrum of stakeholders.

Risk-Sharing Agreements

One concept which is gaining steam much more quickly outside the US, but which will likely migrate towards the US as well, is the emergence of risk sharing deals between payers and industry. One of the most widely publicized such deals involved Velcade treatment in the UK in 2007, wherein Millenium agreed to reduce the price paid for the drug if the health outcomes of those using it initially did not indicate a predetermined level of efficacy. Roche followed suit, inking a deal with NICE for rebates on Tarceva, as did Merck-Serono for Erbitux as well. Other agreements, such as the one between Novartis and the NHS over Lucentis in 2008, differed slightly in that the manufacturer agreed to pay for any treatments required beyond an initial number. An early risk sharing scheme for treating multiple sclerosis in the UK involved a maximum price per QALY for Avonex, Betaferon, Rebif, and Copaxone. GSK created a deal in which they offered a 12.5% price cut and a rebate if their drug failed a head-to-head trial against a comparable drug from Pfizer. Such agreements are gradually pushing their way into the US markets as well, although not currently at a national level. Merck and Cigna have a risk sharing agreement over diabetes drugs, and United Healthcare and Genomic health recently enacted a temporary agreement over a breast cancer diagnostic test¹⁸.

Figure 6: Select risk sharing deals in biotech / pharma

Sponsor	Drug	Counterparty	Year	Details
Multiple	MS drugs -Avonex, Betaferon, Rebif, Copaxone	UK	2002	Maximum price / QALY of £36,000
Novartis	Diovan	US	2004	Patient money-back guarantee
Bayer	Levitra	Denmark	2005	Refunded cost to unsatisfied patients
J&J	Velcade	UK	2007	Reimbursement to healthcare system if tumors did not shrink
Novartis	Lucentis	UK	2008	Pay for all treatments required beyond initial 14
Merck	Janumet / Januvia	Cigna	2009	Discounts to drug prices when successful and compliance
GSK	Votrient	UK	2010	12.5% price cut + rebate if fail H2H vs Pfizer's Sutent

Recent Trends: Drug sponsor to pay for specific adverse events while patient on therapy e.g. SA/P&G deal with Health Alliance to pay for fracture costs for patients on Actonel, Cigna asking drug makers of cholesterol-lowering pills to pay for myocardial infarctions

While these deals provide a potentially valuable way to reduce risk and improve patient outcomes in the future, and may be especially valuable in orphan indications, criticisms abound. For one thing, there is little current evidence that these deals actually result in significant savings for payers. Further, most of the risk-sharing agreements came about due to a coverage or reimbursement rejection of a drug, and consequently there has been little or no standardization among manufacturers or payers on deal parameters, measures of effectiveness, or implementation⁴⁴. In the US, moreover, although CMS has the ability to require “coverage with evidence”, at the moment deals are only struck with individual commercial payers. Going forward, this practice needs to become more widely accepted, especially in the orphan space, where initial trials are necessarily difficult. As indicated above, payers do not balk at paying for valuable treatments which significantly help patients, but proving such effect remains a significant hurdle in many cases. Standardization of risk-sharing processes and outcome measurements can go a long way toward controlling costs and helping to more adequately share value in the healthcare system.

Global Impact

Another challenge facing the orphan market in coming years is the emergence of developing countries onto the global landscape. Current reimbursement procedures are such that it only makes sense to charge for an orphan drug in industrialized countries with advanced payer systems. Often, drug manufacturers find (in non-orphan indications as well) that charging a significantly lower price in a developing country for the same drug can cause a public relations nightmare which is not nearly offset by the added revenue, as US patients argue that they are subsidizing the global pharmaceutical market. This presents a problem for patient-focused companies, as a commitment to leaving no patients without care means that they must then offer many of their treatments for free, while simultaneously pleading with the government to offer full reimbursement. Potentially a deal wherein western NGOs fund drugs for a small percentage of the full price for a group of patients in developing countries would be more palatable than simply discounting the price outright. How these negotiations evolve will play an ever-growing role in the ability of orphan drug manufacturers to command high prices.

Chapter 7: Conclusions

Our results highlight the fact that thought leaders from across the healthcare landscape predominantly do not feel that large scale change will impact the orphan market over the next five years, and certainly not in such a way as to require a significant change to currently employed orphan drug forecasting models. Indeed, it seems fair to conclude that the perceived value proposition of orphan products is unchanging in the near future, as the perspectives of current opinion leaders do not suggest changes to the commercial or political value inherent in such products anytime soon. Even without such dire changes, however, our research has implications for each set of stakeholders in the orphan product space to reexamine unsustainable practices and to take initiative in creating innovation and implementing solutions to some of the serious economic challenges affecting the industry, whether problematic currently or in ten years time. As budgets are constrained across the board, some of this innovation is already occurring elsewhere in healthcare. The Blue Cross Blue Shield Alternative Quality Contract is effectively a more palatable form of capitation and seeks to supplant the fee-for-service model so common in medicine. Physicians are beginning to band together to demand equal discounting for drugs and supplies much like the discounts commonly provided to larger purchasing organizations. Nonprofit organizations, such as the National Quality Forum, are seeking to bring many different stakeholders together to help build consensus on devising national priorities and goals for performance improvement, creating quality measurement systems, improving public performance reporting, and promoting education and outreach programs. Large segments of the healthcare community are thus already recognizing the need for concrete action and leadership, and our results demonstrate that many of those within the orphan community must recognize that there are challenges to be addressed in this space as well.

Challenges for Regulators and Legislators

1. Understand the confusion around the orphan drug pathway and seek to clarify details relating to surrogate endpoints and studies with non-placebo controls.
2. Work with the pharmaceutical industry to create a framework for post-approval studies which will enable patient access to crucial medications more quickly.

3. Pay close attention to emerging technologies such as stem cell and gene therapies and personalized medicine to understand their potentially unintended impact on orphan incentives and costs.
4. Concentrate on easing existing challenges in the orphan space through increased focus on global collaboration for orphan designation and approval, as well as global patient registries.
5. Standardize control of orphan drug incentive misuse, either through direct legislative/regulatory changes, or through government sponsored trials of the generic drugs often used for off-label treatment.
6. Allow CMS more power in negotiating pricing decisions, in balance with continuing to adequately incentivize industry to deliver innovative medical treatments.
7. Strive for transparency in discussing issues with orphan drug pricing from both an emotional and an economic perspective, always involving multiple stakeholders in discussions.

Challenges for Payers

1. Take a more active role in understanding actual medical impact of orphan drugs through improved outcomes and research focused databases, despite the limited budgetary impact these diseases currently represent.
2. Begin to standardize and insist more widely on risk-sharing deals and their accompanying outcome measures, to help offset costs in a politically acceptable way.
3. Endeavor to better understand how increases in copayments and coinsurance rates impact access to orphan drugs and understand the indirect consequences of attempting to shift costs in this way.
4. Collaborate with industry to determine (for all drugs) which pharmacoeconomic factors are valuable in assessing drug performance, and assist with designing trials and databases to meet those goals.

Challenges for Patients, Patient Advocacy Groups, and Providers

1. Understand the impact of impending funding shortages for research in ultra-orphan indications and pursue alternative methods for designing treatments for these diseases, such as incentivizing pharmaceutical companies to open up massive candidate libraries to the NIH for high throughput screening.
2. Strike a balance between pushing for new treatments to emerge as quickly as possible, even with marginal efficacy, and the indirect costs which such speed may have on funding for other diseases.
3. Work with payers and industry to determine what steps may be taken to reduce the growing cost burden on patients, and understand quantitatively how that increasing burden is impacting patients' access to drugs.

Challenges for Industry

1. Adjust to the impending reality that less effective drugs may be rejected or covered at a lower cost, but will inevitably require better data validation for pricing.
2. Work with payers, both commercial and government, to help create trustworthy pharmacoeconomic assessments, and thereby help justify pricing in the eyes of payers as well an increasingly skeptical public.
3. Engage the orphan market globally, helping to treat patients outside of developed countries in a way which earns revenue while minimizing public relations damage, thus helping to offset cost pressures in the US.
4. Lead the way by standardizing risk-sharing deals with US payers and proactively offering such deals (not simply post-rejection) as proof of value added.

Appendix A: Interview Contacts

- Andrew Curtis, Strategy / Innovations for Biotherapeutics (formerly head of Rare Disease Unit), Pfizer
- Andrew Tager, M.D., Mass General Hospital
- Bill Kassler, Chief Medical Officer- New England Region, CMS
- Bill McColl, Political Director, AIDS Action
- Catherine Courtin, Launch Brands, Biogen Idec
- Chris Hren, Global Hemophilia Marketing, Biogen Idec
- David Caponera, Access Services, Pfizer
- David Gilman, Partner, The Frankel Group
- David Miller, Market Access, Biogen Idec
- Dee Simons, Government Reimbursement Policy, Biogen Idec
- Diane Dorman, VP of Public Policy, National Organization for Rare Diseases
- Diego Sanchez, Legislative Assistant to Congressman Barney Frank
- Edwin Choy, M.D., Mass General Hospital
- Elkan Gamzu, former CEO, Cambridge Neuroscience
- Gayle Silverman, Portfolio Maximization, Pfizer
- Howard Moy, Direct Market Access, Pfizer
- Jan Cook, Medical Director- Medical Innovation and Leadership, Blue Cross Blue Shield of Massachusetts
- Jeff Fritch, Regulatory Review Officer, FDA Office of Orphan Product Development
- Jim Coccia, Commercial Decision Support, Genzyme
- Jim Hancovsky, VP Pharmacy, United Healthcare
- Jonathan Gertler, Partner, Back Bay Life Science Advisors
- Julie Kerner, New Product Commercialization, Biogen Idec
- Mara Aspinall, CEO On-Q-ity (formerly president of Genzyme Genetics)
- Matt Trudeau, Global Marketing, Biogen Idec
- Michael Schmidt, Analyst, Leerink Swann
- Mike Poirier, Regulatory Affairs, Biogen Idec
- Rob Brekosky, Pharmacy Program Operations Director, United Healthcare
- Susan Maddux, National Director, United Healthcare
- Tim Cote, Director Orphan Products, FDA
- Vikas Sukhatme, Chief Academic Officer, Beth Israel Deaconess

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Additional Notes

- A. Mark Merritt, chief executive of the Pharmaceutical Care Management Organization explained that use of these “pay-cards” by industry is short-sighted since plans will inevitably find ways to limit their use.

- B. This question was deliberately phrased in a harsh light in order to evoke significantly divergent responses from the various stakeholders interviewed.