



# Innovative Pricing Models Potentially Drive Payer Coverage: A Market Access Case Study for RNAi Therapeutics

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Innovative Pricing Models Potentially Drive Payer Coverage:  
A Market Access Case Study for RNAi Therapeutics

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A Thesis in the Field of Biotechnology Management  
For the Degree of Liberal Arts in Extension Studies

Harvard University

March 2017

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## Abstract

The objective of this thesis is to establish a strong understanding of the US payer landscape and key influencers in the orphan disease space. This investigation will also provide a foundational understanding of the payer perspective on novel RNAi therapeutics and how innovative, value-based pricing structures can potentially drive payer coverage for such products. Through primary research with payers and experts in the field, as well as a literature review, we aim to answer the following key questions:

1. What is the current payer environment for orphan drugs launched in the US?
2. What drives willingness to pay for orphan products today and in the future?
3. What potential innovative structures (such as Performance-Based Risk Sharing Agreements, PBRsAs) could exist for RNAi therapeutics?

The key findings suggest that establishing novel reimbursement arrangements may be challenging, however there does exist potential for such arrangements to be implemented under the right set of circumstances. The structure of such arrangements will need to be straightforward and easily administered. Early discussions and continued proactive interactions, including targeted payer engagement from Phase II clinical development through post-approval, should be leveraged in order to best understand payer needs and develop robust evidence packages. Finally, expanded market access and medical affairs teams will be essential to educate the intricate network of influencers and payers, develop value propositions that resonate with key stakeholders, and ensure the novel RNAi mechanism is reasonably well understood.

Recommended actions to bolster the likelihood of success with innovative, performance-based agreements may include the following:

(a) Conduct studies to tie target knockdown to clinically meaningful outcomes and to understand potential inter-patient response variability;

(b) Draft potential contracting schemes considering areas of greatest uncertainty;

(c) Develop outreach plans prioritize education of the payers most willing to be innovative and leaders in the industry.

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## Chapter I

### Introduction

In September 2015, the pharmaceutical and biotech sectors came under fire by politicians for price gouging when Turing Pharmaceuticals raised the price of their drug, Daraprim, by 5,000% to \$750 per pill, overnight. Biotech CEOs say the conversation should focus less on placing blame and more on finding a proper balance in drug prices that allows for innovation and affordability (Lenzo, 2016). Nonetheless, each payer has a finite amount of money to cover an infinite amount of potential healthcare interventions, thus some form of prioritization of healthcare spend is typically implemented.

Alnylam Pharmaceuticals, Inc., a leading biopharmaceutical company developing innovative RNA interference (RNAi) therapeutics, is potentially uniquely poised to address pricing issues as they emerge as a new commercial stage company over the coming 2-3 years. Alnylam Pharmaceuticals is taking proactive steps to become an industry leader in market access. This thesis supports a foundational effort to better understand the US payer landscape (Figure 1, Appendix) and thought-leader network for targeted education and engagement efforts around novel RNAi therapeutics, such as those residing in Alnylam's portfolio.

Alnylam CEO, John Maraganore, has publically championed the adoption of pay for performance (P4P) pricing, a pricing structure where drugs are priced based on anticipated value; if that value is not achieved in the real world setting, a rebate or discount may be issued (Belvedere, 2016). While P4P has been successfully implemented

for a handful of therapies (more commonly in some European countries where the information technology infrastructure to support administration of such schemes may be more advanced), the widespread adoption of P4P across the EU or US continues to be challenging. The complex and fragmented payer network in the US, as shown in makes the design and execution of such arrangements potentially more challenging (Garrison *et al*, 2013). However, there have been some examples of successfully implemented performance-based agreements in the news recently.

The objective of this thesis proposal is to develop a deeper understanding of the US payer thought-leader network. It will also provide a foundational understanding of payer response to the novel RNAi modality and how innovative, performance-based pricing structures can potentially drive payer coverage for such products.

The main questions we intend to explore are the following:

1. What is the current payer environment for orphan products launched in US?
2. What drives willingness to pay for orphan products today and in the future?
3. What potential innovative structures (such as Performance-Based Risk Sharing Agreements, PBRsAs) could exist for siRNA therapies?

The project methodology employed primary, secondary, and case study research to identify the payer influencers and ascertain how innovative pricing structures may drive payer preferences. We aim to understand what characteristics of such structures would support successful implementation and sustainability. We will also highlight key areas of organizational design and engagement that may be useful supporting this approach.

## Chapter II

### Background

This section introduces the entities (government, pharmaceutical, insurance payers) comprising the healthcare system and details the current drug pricing climate.

This section reflects upon the successful implementation of previous pricing arrangement literature and introduces the biotechnology of RNAi, which could potentially benefit from these pricing arrangements.

### The Need for a Change in Pricing Approach

Pharmaceutical companies are an incredible source of American innovation and revolutionary treatments for debilitating diseases. However, many argue that these same technologies have contributed to the dramatic rise in health care spending (NEHI, 2012). Drug pricing is a problem that transcends all political parties, as nearly three-quarters of Americans think drug prices are unreasonably high and most blame drug companies' drive for profits (Norman, 2016). The media has highlighted the unsavory pricing practices of Turing Pharmaceuticals, Valeant, and Mylan, sparking public outrage throughout the 2016 presidential race. This is not an isolated problem; between 2008 and 2015, drug makers increased the prices of almost 400 generic drugs by over 1,000 percent. These companies are examples of a troubling trend, in which manufacturers acquire off-patent drugs and raise the price (Karlen-Smith, 2016). Most notably, Turing Pharmaceuticals acquired Daraprim, a 62-year-old drug used to treat a serious parasite

infection, and increased the price by 5,000%, from \$13.50 to \$750 per pill overnight. Turing's decision catalyzed biotechnology stocks to fall broadly as investors worried about possible government action to control pharmaceutical prices.

Mylan is the latest pharmaceutical company to draw criticism for its recent price hike of EpiPen, the lifesaving device carried by millions of people with severe allergies. Since Mylan acquired the drug in 2007, it has raised the price six-fold to \$600, from \$100 (Thomas, 2016). Despite its monopoly on the product, EpiPen is a generic drug. As a generic instead of a branded drug, EpiPen can be sold with a smaller discount to the states. The classification of the EpiPen has added a new wrinkle to the intense scrutiny of its pricing and has raised questions about how closely the federal government is overseeing the pricing of drugs paid for through government health programs. The classification is significant because owners of generic drugs pay rebates of 13 percent of the average manufacturers' price. But manufacturers of brand-name drugs must offer discounts of about 23 percent off that average price, or the difference between the average price and the best price they have negotiated with any other US payer, whichever gives the bigger discount. In addition, brand-name manufacturers must pay more in rebates if their products' prices rise faster than inflation, as EpiPen's did (Thomas, 2016).

As US drug prices rise, some drug makers are playing down their role, instead heaping blame on the middlemen who help determine how medicines are priced. Critics such as Heather Bresch, chief executive officer of Mylan, says her company is being treated unfairly for a dysfunctional system in which wholesalers, pharmacies and Pharmacy Benefit Managers (PBMs) take their own cut of each prescription (Walker, 2016). PBMs oversee drug-benefit plans for employers and hold down the cost of

providing those benefits, which they do by choosing which drugs to cover and using that leverage to wrest lower prices from drug makers through rebates. However, these rebates are based on a percentage of a drug's list price, and PBMs have benefitted as the price of drugs has skyrocketed in recent years. These rebates can also encourage drug companies to increase prices more sharply than they would have done otherwise. PBMs deny that they cause drug-price inflation, saying drug costs would be even higher without rebates (Walker, 2016).

Hillary Clinton cited EpiPen as she unveiled a proposal on September 2, 2016 to curb excessive price increases on drugs, in part by creating a federal consumer oversight body that would investigate and respond to price hikes of older drugs with limited competition, as was the case with Mylan's EpiPen. The board could wield enforcement, fines or increased rebates, when it determines a price increase is unjustified. That money would be used to support new programs to make lower-cost alternatives available and increase approval of competing treatments (Hillary Clinton Factsheet, 2016). The campaign compared the idea to the Vaccines for Children program, which directly purchases and distributes vaccines to ensure their availability. Clinton said this will incentivize new companies to enter the market and put downward pressure on drug prices. The plan would also allow for the temporary importation of drugs from other countries. Mrs. Clinton's proposals may have been a solid start to fixing the drug pricing system, as Americans should be able to afford prescriptions for their conditions throughout the year, and avoid interruptions to treatment.

Drug pricing reform is of utmost importance in cases of rare genetic disorders, where life-saving medicines come with burdensome costs, as it is commercially

challenging to develop drugs for a very small number of patients. Nevertheless, scores of companies, ranging from the giants in the pharmaceutical industry to tiny venture capital-backed biotech startups, are targeting disorders that in some cases are so rare that they affect only a few hundred patients in the United States. When we have so many other pressing health care problems to confront, why has the orphan drug initiative grown so fast? And why does it make sense, both clinically and socially, for our society to pay for the rising number of expensive therapies? In short, the 1983 Orphan Drug Act provided special tax incentives and market benefits to companies that successfully developed new drugs for diseases that afflict fewer than 200,000 Americans (about 1 in 1500). The debate is currently focused on paying for costly breakthrough drugs and is being played out in state Medicaid programs, where the federal government provides about half of the funding. This means the costs of paying for these drugs are ultimately borne by the taxpayers (Reilly, 2016).

Dr. Philip Reilly, a Boston based venture partner and author of *Orphan: The Quest to Save Children with Rare Genetic Disorders* explains why the cost of treating orphan disorders may still be a bargain in the long-run:

The price of new drugs to treat rare genetic disorders, frequently called “orphan” diseases, has been debated periodically for four decades. And the recurring question has been, “Can we afford these treatments?” In the 1970s, the discussion focused on the cost of treating boys with hemophilia, as it was sometimes more than \$300,000 a year if the child required high doses of drugs. In the 1980s, it centered on bone marrow transplants, which today cost about \$200,000, and in the 1990s and 2000s, it focused on enzyme replacement for disorders like Gaucher disease and Fabry disease (about \$250,000 a year). Some of the drugs emerging now, and some that are likely to come soon from gene therapy and gene editing, may cost as much as \$1 million per patient or more (Reilly, 2016).



Reilly says there are three principal reasons why these drugs will be so expensive:

1. They require millions of dollars to develop; 2. The diseases they target are very rare; 3.

A single treatment might be sufficient to stabilize or reverse the disease- an intervention unlike anything in the history of mankind. Dr. Reilly acknowledges that it is natural to cringe at the charges for these treatments and the temptation to decry the industry for price gouging. He urges us to ask what the cost of not developing these drugs:

For many of the hundreds of severe single-gene disorders, the cost of “supportive care” (usually the only option) is extremely expensive, but this care does not end in either disease stabilization or a cure. Of course, the cost to a family of watching a child suffer for years before dying is incalculable. We are well into a new era of drug development that will greatly improve the prospects for cures for many non-genetic diseases. The field of cancer care is in a golden age, with many new therapies (often keyed to a “driver” mutation in the tumor’s DNA) entering the market at a cost of about \$100,000 per patient and extending life by a few months to a few years. These treatments are mostly used by older people. Spending \$1 million to restore a full life to a young child may well generate a better return on investment to society than spending one-tenth of that on an elderly cancer patient. We are all at risk for cancer, and we are all at risk for having a family member diagnosed with a rare genetic disease. If shown to be effective, new therapies for orphan genetic disorders may confer 70 years of normal life to a child (Reilly, 2016).

The United States is about to radically change how it pays for health care, as the need to fix healthcare and provide affordable drugs to patients with life-threatening diseases is urgent. Drug pricing issues involve not just drug companies but entities such as pharmacy benefit managers, insurance companies, wholesalers, pharmacy chains and hospitals, taking profits out of the value chain and each adding expense to the overall healthcare system. To begin to deal with drug pricing issues effectively, we must insist on pricing transparency from all these entities. Only when we know where each dollar of a drug’s list price is going will be able to begin to make constructive changes to the system (Cohen et al., 2016).

## Drug Pricing Trends

Despite ongoing reform efforts, U.S. expenditures on healthcare as a percentage of GDP are still rising. Drug prices are increasing at an unsustainable rate without any sign of abating (Figure 2, Barreuta, 2015). Prescription drug spending, defined as expenditures on prescriptions medicines and over-the-counter products, increased 12.2% to \$297.7 billion in 2014, faster than the 2.4% growth in 2013. The Organization for Economic Cooperation and Development (OECD) estimates 10% of total healthcare spending is attributed to prescription spending in the United States (Stevens, 2014). Health spending is projected to grow 1.1 percent faster than Gross Domestic Product (GDP) per year from 2014-2024; As a result, the health share of GDP is expected to rise from 17.4 percent in 2013 to 19.6 percent by 2024 (NHE Factsheet, 2014). Given the Affordable Care Act's coverage expansions and premium subsidies together with population aging, federal, state and local governments are projected to finance 47 percent of national health spending by 2024 (NHE Factsheet, 2014). This provides great motivation to investigate and challenge the US healthcare expenditure in a comprehensive manner, including expenses incurred in the hospital and physician setting, insurance practices, and drug pricing.

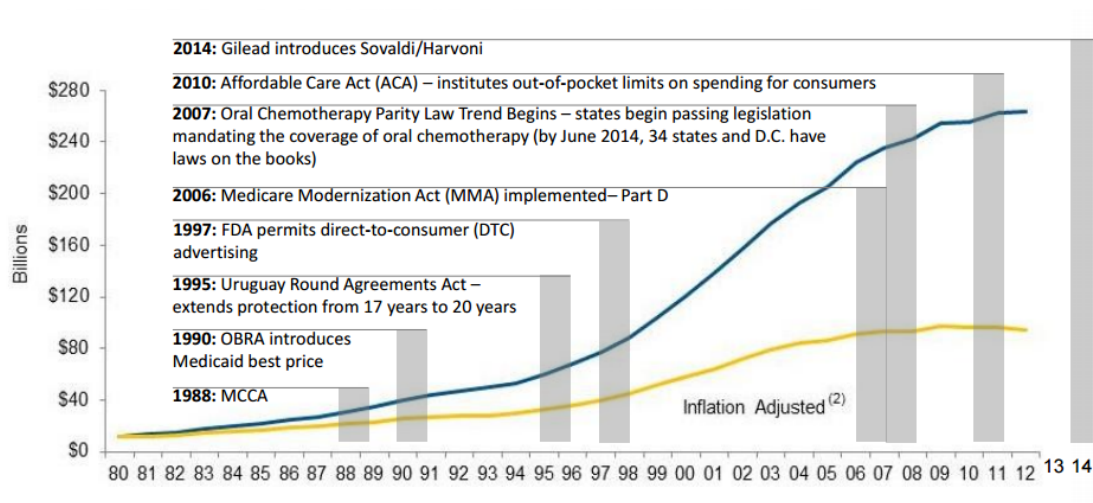


Figure 2. Total Prescription Drug Spending, 1980-2012. Expressed in 1980 dollars; adjusted using the overall Consumer Price Index for All Urban Consumers (Barreuta *et al*, 2015).

Public and private conversations on the pricing issue veer towards “managing” the problem of the cost, by calling for more clinical evidence, creating new regulations around how to manage care for patients, and how to help patients with co-insurance costs. Tony Barreuta, senior vice president of government relations at Kaiser Permanente (an integrated managed care consortium) believes the problem cannot simply be solved by withholding clinically appropriate treatments, more research, or eliminating cost sharing. The pricing model element stands in the way of achieving the public health benefits that these drugs promise (Barreuta *et al*, 2015). Barreuta challenges the current Big Pharma paradigm to develop itself: without protection of market dominance and resulting high profit levels, innovation dies. He suggests asking the following questions: 1. Is the problem of drug pricing best discussed as a public health or insurance coverage problem?

2. Who decides the meaning of value? Payers or manufacturers? Societal norms? 3. Is it time for a new social contract when it comes to patent rights and market exclusivity (Barrueta, 2016)?

### Ongoing Themes in Healthcare Reform





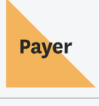
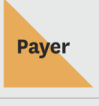






Recent studies reveal inadequate, unnecessary, uncoordinated, and inefficient care and suboptimal business processes eat up at least 35% (more than \$1 trillion) of the amount spent annually on health care. The fee-for-service system, the dominant payment model in the US and many other countries, is now widely recognized as perhaps the single greatest obstacle to improving health care delivery. Fee-for-service makes payments for individual procedures and services, rather than for the treatment of a patient's condition over the entire care cycle. This means multiple independent providers are involved in each patient's treatment, resulting in poorly coordinated care, duplicated services, and no accountability for health outcomes. The big question is: What should replace it? The two leading models are bundled payments and capitated payments (Harvard Business Review, 2016).

In a bundled payment system, providers are paid for the care of a patient's medical condition across the entire care cycle- that is all the services, procedures, tests drugs, and devices used to treat a patient. The accountability built into bundled payments ensures the systematic measurement of outcomes at the condition level, where it matters most. By encouraging competition for the treatment of individual conditions on the basis of quality and price, bundled payments also reward providers for standardizing care pathways, eliminating services and therapies that fail to improve outcomes. The result of

these measures will be actual cost reduction, with studies suggesting savings of 20%-30% in many conditions (Harvard Business Review, 2016). Critics argue bundled payments are too complicated to design, negotiate, and implement, leading many hospital systems, group purchasing organizations, and private insurers to prefer capitation.

In capitation, the healthcare organization receives a fixed payment per year per covered life and must meet all the needs of a broad patient population. It fundamentally shifts the role of managing the amount, form, and cost of care from insurers to medical practitioners. Harvard University professors Porter and Kaplan criticize capitation's top-down approach citing that it does not change health care delivery, nor does it hold providers accountable for efficiency and outcomes where they matter to patients. Capitations savings also come at the high cost of restricting patient choice and inhibiting provider competition. Brent James, MD, Intermountain Healthcare's Chief Quality Officer argues capitation is the only approach that would encourage healthcare providers to attack all types of waste. To understand what's driving up healthcare spending, it's crucial to examine whether, and to what extent, health care payment methods encourage or discourage waste reduction (Table 1). An optimal payment method must address two important challenges: 1. How do we divvy up the savings generated by eliminating waste? If most or all of it goes to providers, how do you ensure that they pass on some of it to customers, especially if there is no efficient market? 2. How does a payment method affect the power of patients and their physicians to make decisions that are in the patients' best interests?

Table 1. Who Gets the Savings from Waste Reduction? (Harvard Business Review, 2016)

TYPE OF WASTE	% OF ALL WASTE	PAYMENT METHODS			
		Cost-plus	Fee for service	Per case	Population-based payment
<b>Production level</b> Inefficient production of individual care units, such as drugs, tests, nursing support	5%	 Payer	 Provider	 Provider	 Provider
<b>Case level</b> Use of unnecessary or suboptimal services in treating a case	50%	 Payer	 Payer	 Provider	 Provider
<b>Population level</b> Unnecessary or avoidable patient cases	45%	 Payer	 Payer	 Payer	 Provider

With most health care payment methods, much of the potential savings from reducing waste would go into the pockets of payers (mainly insurers and to a lesser degree, employers and patients), not to the care delivery groups behind the quality improvement initiatives. Population-based payment is the only system that allows groups to benefit from reducing all three categories of waste, X, Y, and Z. (Harvard Business Review, 2016). This has major implications for health insurers: By removing care oversight from their purview, it only leaves traditional insurance functions such as claims processing, risk analysis, reinsurance, marketing and customer service. It also ensures providers receive enough of the savings so they can afford to fund the changes needed to bring down costs. This is essential; to raise quality and eliminate waste, care providers have to develop innovative new processes, which requires investment.

## Opportunities for Shaping the Dialogue

One essential aspect to understand is how the US payer landscape is intricately structured and influenced. Particularly for rare diseases where the burden of illness and cost of care are not well established, the network of players around the US payers may shape an emerging product's success. This network is a collection of commercial insurance providers, academicians, government agencies, trade associations, patient advocacy groups, and clinical thought-leaders, which can provide expert insight, education and engagement about diseases and potential therapies. But understanding how these players work together to drive decision-making across the industry, early seeds may be planted and cultivated over time to optimize the development and commercialization of novel therapies, such as RNAi therapeutics.

Let us begin with an overview of key health insurance providers. Blue Cross Blue Shield Association (BCBSA) plans and other major commercial insurers account for 50% of covered lives (3.). These commercial payers provide either fully-insured or self-insured plans to US employers. Fully-insured plans assume financial risk for any medical/pharmacy claims, in addition to administration of benefits and services. Large employers may often self-insure, taking on the financial risk themselves while contracting with a payer to administer a set of benefits. United, Anthem, and Aetna are the next largest commercial payers and, along with several PBMs, are likely to have a higher number of patients suffering from a given orphan disease.

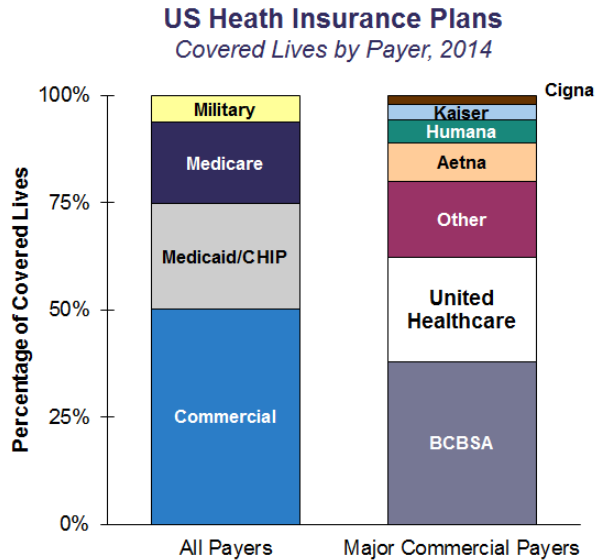


Figure 3. United States Health Insurance Plan Payers (Health Advances Interviews and analysis, company websites, 2015 Avenir Managed Care Digest, Congressional Budget Office, Kaiser Family Foundation, Mark Farraiah Associates)

The remainder of covered lives is split between government plans: Medicare and Medicaid and the Children’s Health Insurance Program (CHIP). Medicare is the federal health insurance program for people who are 65 or older, certain younger people with disabilities, and people with End-Stage Renal Disease (permanent kidney failure requiring dialysis or a transplant, sometimes called ESRD). There are various parts: Part A covers inpatient hospital stays, care in a skilled nursing facility, hospice care and some home health care. Part B covers certain doctor’s services, outpatient care, medical supplies, and preventive services. Part C (Medicare Advantage Plus) includes Health Maintenance Organizations, Preferred Provider Organizations, Private Fee-for-Service Plans, Special Needs Plans, and Medicare Medical Savings Account Plans. The Medicare Advantage Plans may also offer prescription drug coverage that follows the same rules as



Medicare Prescription Drug Plans. Part D adds prescription drug coverage to Original Medicare, some Medicare Cost Plans, some Medicare Private-Fee-for-Service Plans, and Medicare Medical Savings Account Plans. These plans are offered by insurance companies and other private companies approved by Medicare. (Medicare.gov, 2016)

Medicaid/CHIP provides free or low-cost health coverage to millions of Americans, including some low-income people, families and children, pregnant women, the elderly, and people with disabilities. CHIP specifically provides low-cost health coverage to children in families that each too much money to qualify for Medicaid. Medicaid programs must follow federal guidelines, but coverage and costs may be different from state to state. Some Medicaid programs pay for care directly while others use private insurance to provide Medicaid coverage Medicaid/CHIP enrollment has increased by 25% since the Affordable Care Act went into effect. (Healthcare.Gov, 2016).

The Medicaid Drug Rebate Program includes the Centers for Medicare and Medicaid Services (CMS), State Medicaid Agencies, and participating drug manufacturers that help to offset the Federal and State costs of most outpatient prescription drugs dispensed to Medicaid patients. Approximately 600 drug manufacturers currently participate in this program. All fifty States and the District of Columbia cover prescription drugs under the Medicaid Drug Rebate Program. The program requires a drug manufacturer to enter into, and have in effect, a national rebate agreement with the Secretary of the Department of Health and Human Services (HHS) in exchange for state Medicaid coverage of most of the manufacturer's drugs. When a manufacturer markets a new covered outpatient drug, it must also submit product and

pricing data concerning the drug to CMS via the Drug Data Reporting for Medicaid (DDR) system. This ensures that states are aware of the newly marketed drug.

Manufacturers are required to report all covered outpatient drugs under their labeler code to the Medicaid Drug Rebate Program. Manufacturers are then responsible for paying a rebate on those drugs for which payment was made under the state plan. These rebates are paid by drug manufacturers on a quarterly basis to states and are shared between the states and the Federal government to offset the overall cost of prescription drugs under the Medicaid Program.

The Academy of Managed Care Pharmacy (ACMP) believes that the best price provisions of the Medicaid prescription drug rebate program represents interference by the government into the competitive marketplace that has raised costs unnecessarily by preventing the commercial market from allowing true market dynamics to emerge. While the government has a responsibility to protect consumers against anticompetitive activity, the government must not establish rules that have the unintended effect of undermining competition. In the private market, purchasers with sufficient market power can demand that they be provided the best price for a particular item that a seller might offer to any other purchaser. Under the antitrust laws, such “most favored nation” provisions could have serious legal ramifications if they have the effect of restricting or destroying competition, whereas smaller purchasers are unable to negotiate lower prices because the seller is unwilling to offer the same price to the larger purchaser. This has the effect of reducing competition and raising prices (ACMP, 2009).

This is precisely what happened with the implementation of the best price provisions of the Medicaid drug rebate program (GAO, 1994). This law requires brand

name drug manufacturers to provide the Medicaid program with the lowest price they offer in the rest of the drug marketplace. Prior to the law's enactment in 1990, health maintenance organizations (HMOs), hospital systems and other well-organized purchasers had been able to negotiate deep discounts – often greater than 50%. In the immediate wake of the law's passage, rather than extending these deep discounts to Medicaid, drug manufacturers instead terminated discount contracts to HMOs and hospitals. Manufacturers became disinclined to offer smaller purchasers discounts and incentives that would then apply to a nationwide market such as Medicaid, which represented a much larger share of the total market than any single HMO or hospital system. The ACMP endorses alternative solutions: Congress could replace the best price formula with a flat percentage rebate that generates the same level of savings for the Medicaid program that they have experienced for the past 19 years. The Medicaid program could continue to benefit from the same rebates that protect against excessive inflation of drug costs, which generates a substantial portion of the rebates paid today. Congress could also repeal the best price program and allow market forces to determine pricing (ACMP, 2009).

In rare diseases, payers are likely to consult Key Opinion Leaders (KOLs) to assess clinical value and estimate demand. Also known as clinical thought leaders, KOLs are the experts in their field upon whom we depend for original research leading to disease understanding, diagnostic and treatment guidelines, and the unmet medical need. Pharmaceutical companies generally engage KOLs early in the drug development process to gauge advocacy activity and elicit key feedback on potential development and commercialization strategies. Physician KOLs can be an important resource to

pharmaceutical companies and device manufacturers. They provide insights and understanding regarding treatments and support programs that most benefit patients. They can contribute throughout the product life cycle, from research and development to marketing programs. They may participate in guiding the design of relevant, outcomes-based clinical studies or help the organization understand habits and motivations for prescribing or recommending one device or drug over another (Capper, 2016).

In some cases, panels of KOLS are assembled for clients. The advantage of KOL panels is the convenient access to a panel of experts on an ongoing basis. Members of KOL panels are often involved in qualitative interviews and questioning. Sometimes trends can be uncovered by consistent and repeated questioning of a panel over time. If Ad hoc engagements with KOLs involve face-to-face or telephone interviewing. In these cases, the respondent is provided questions in advance of the interview, allowing time to properly prepare and raise any objections in advance of the interviews. The organization usually determines what the expert will receive in return for their participation. The benefit to the expert participant may vary from one KOL to the next and may include the following: Access to unpublished data, clinical trial opportunities, training/education, sponsorship of research (Capper, 2016).

Trade organizations are the remaining entities of the payer thought-leader network. Pharmaceutical-related trade organizations are founded and funded by businesses that operate in the healthcare industry and engage in public relations activities such as advertising, education, political donations, lobbying and publishing, with a focus on collaboration between companies. They are often non-profit organizations, governed by bylaws and directed by officers who are also members. One of the primary purposes

of trade groups in the United States is to influence public policy in favor to the group's members. Associations may offer other services such as producing conference, networking, charitable events, and offering classes or educational materials. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) is a US organization that represents biopharmaceutical and biotechnology companies. Their mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies (PhRMA.org, 2016). Another example is the National Organization for Rare Disorders (NORD). Their goal is to improve the lives of individuals and families affected by rare diseases. NORD provides services for patients and their families, rare disease patient organizations, medical professionals, and those seeking to develop new diagnostics and treatments (NORD, 2016).

### Introduction to Innovative Pricing Schemes

At the time of initial product launch, the real-world clinical and economic performance of that product is largely unknown. The concomitant financial risk to the payer for a new treatment that does not work as anticipated has increased along with the rising price of the new treatments. If payers are reluctant to adopt new products due to this uncertainty, manufacturers face the risk of delayed uptake and reduced revenue. As a result, there is a significant and growing interest across the industry, and the world, for innovative contracting agreements where the financial outlay for a product is more closely tied to its actual performance in the real-world setting.

US payers and manufacturers can form a variety of agreements to manage total budget impact, drive appropriate use, or mitigate uncertainty in performance. The two over-arching types of agreements include financial-based pricing arrangements and performance-based risk-sharing arrangements (Figure 4, Morel, 2013).

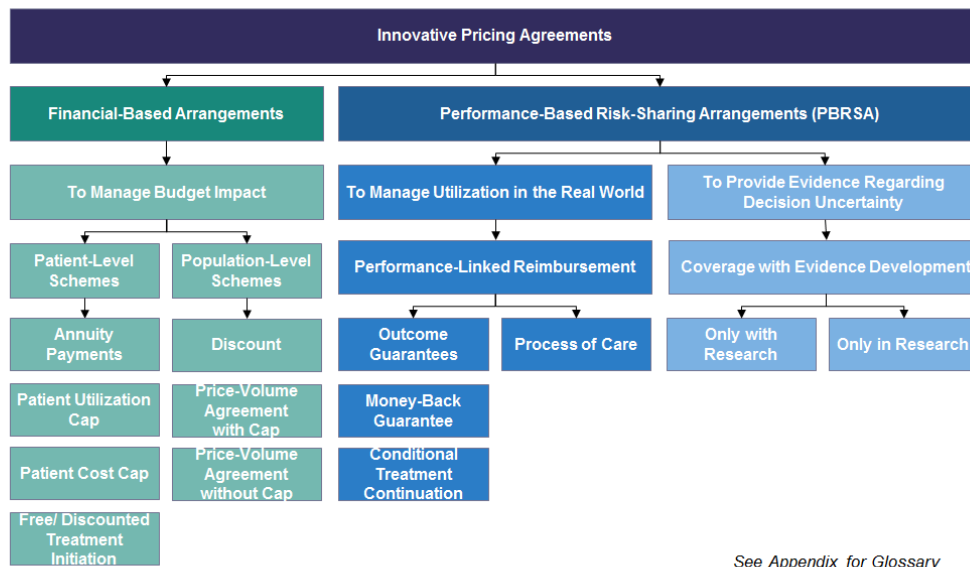


Figure 4. Innovative Pricing Arrangements for US payers and manufacturers (Morel, 2013)

Financial-based schemes often have little to do with patient outcomes, concentrating more on keeping expenditures within agreed upon limits. Some of the more common tools include the following:

- Discounts are a deduction from the typical price of a therapeutic.

Pharmaceutical manufacturers may issue a negotiated discount to payers, on an individually contracted basis, to gain coverage under that specific plan or within a specific country.

- Price-volume agreements focus on controlling financial expenditure by requiring the pharmaceutical companies to refund the insurer if annual sales exceed a predetermined threshold;
- Patient Cost Caps focus on controlling the financial impact from an individual patient perspective; if for some reason a specific patient requires more drug than is expected, the incremental doses may be provided at no cost
- Free Treatment Initiation may be implemented to limit financial exposure for the payer before the drug has reached full efficacy

Alternatively, performance-based risk-sharing schemes typically involve an agreed upon clinical measure, hospitalizations for example, and then a financial impact based on the achievement or lack of achievement of reaching that measure.

- Outcomes Guarantees are when payment is required for responders to medication only.
- Coverage with Evidence Development (CED) is a possibility when a payer covers a drug or services with the expectation that ongoing evidence development will support specific economics or clinical assumption; as more evidence becomes available, the coverage decision is reassessed.

Performance-based risk-sharing arrangements (PBRsAs) represent one mechanism for reducing uncertainty through greater investment in evidence collection while a technology is used within a health care system, post-approval. PBRsAs involve a plan where the performance of the product is tracked in a defined patient population over a specified period of time and the amount or level of reimbursement is based on the health and cost outcomes achieved (Garrison, 2013). Any number of stakeholders may be

involved in developing PBRsAs, including drug and device manufacturers, public and private payers and insurers, employers financing insurance, hospital and physician providers, central pricing authorities, and regional budget-holders. Agreements often also include some aspect of patient responsibility where compliance to the therapeutic regimen is recommended.

Payers need to assess how the introduction of a new therapy will change patient care in the future compared to what is the standard of care today. The fundamental motivation for a PBRSA is that the manufacturer and the payer hold different views regarding the potential value of that new intervention. The concept of uncertainty around that value influences payer's willingness to pay for it. The manufacturer wants a higher price (or utilization than the payer thinks), while the payer is concerned about "decision uncertainty"- the probability of paying for a product that might not be effective or cost-effective in some or all of the patients who receive it following adoption in their health care system (Griffin, 2011).

Investment in a PBRSA should lead to an arrangement that will better align the rewards desired by the manufacturer with the value that the patients (represented by the payers) would assign to the new intervention if the outcome was more certain. To evaluate the decision of additional investment, manufacturers compare the costs of the additional evidence generation with the potential benefits of the new data and how it can better enable payers in terms of making improved resource allocation decisions.

The International Society for Pharmacoeconomic Outcomes Research (ISPOR) lists the key characteristics defining a PBRSA: 1) A system of data collection is agreed upon between the manufacturer and the payer. It may be required by the payer to address



uncertainties about long-term effectiveness (beyond trial duration and including unintended or adverse consequences), reducing uncertainty about the expected cost-effectiveness of a medicine (or device or diagnostic) in the health care system. The data collection can be organized in patient group/population-based studies or by tracking individual patients. 2) The data collection is initiated during the time period following the regulatory approval and linked to post launch coverage decisions. It is directed at informing payers, providers, and prescribers as decision makers. 3) The price, reimbursement, and/or revenue for the product are linked to the outcome of this program of data collection, either explicitly by a pre-agreed rule or implicitly through an option to renegotiate coverage, price, or revenue at a later date. In some cases, reimbursement is linked directly to the performance of the drug in a particular patient- a form of an individual performance guarantee. 4) The data collection is intended to address uncertainty (ex. efficacy or effectiveness in the tested population as compared with the current standard of care). 5) PBRSA provide a different distribution of risk between the payer and the manufacturer than does the historical manufacturer-payer relationship (Garrison, 2013).

The process for deciding when to engage in a PBRSA has been opportunistic and ad hoc. Many agreements remain confidential; however, the existence of more than 20 examples may be cited in the United States. Major health care payers, including United Healthcare, Cigna, and Harvard Pilgrim Healthcare, as well as pharmaceutical manufacturers such as Merck, Novartis, Amgen, and Sanofi-Aventis, have demonstrated a willingness to engage in performance-based schemes.

Recently, Harvard Pilgrim announced two separate performance-based deals. One was reached with Novartis for the congestive heart failure drug, Entresto. The second deal, with Eli Lilly, was based on their diabetes drug, Trulicity (Modern Healthcare, 2016). Novartis has priced Entresto at \$12.50 per day. Patients with congestive heart failure typically incur hospitalizations as a result of poorly managed or progressing disease. Harvard Pilgrim will receive a confidential discount on Entresto, not unlike that which most other major insurance plans in the US typically negotiate with manufacturers. However, if Harvard Pilgrim patients on Entresto do not achieve an agreed-upon rate of hospitalizations, the performance of Entresto will then be determined to not achieve the anticipated real-world benefit. In that case, the insurer will receive an additional rebate.

Under the Lilly agreement, Harvard Pilgrim has made the drugmaker's type 2 diabetes drug, Trulicity, a preferred drug in exchange for a discount if it performs better than competing drugs. Trulicity normally costs \$574.80 for a 28-day regimen, according to Lilly spokesman Greg Kueterman. He stated the company stance on the arrangement, "Hopefully patients will be getting treatment that benefits them in the most optimal way. The payer will have members who are getting better treatments, and Lilly has contract terms that are better than they otherwise would be."

In addition, Harvard Pilgrim previously entered a risk-based contract with Amgen for the cholesterol lowering drug Repatha. In addition to providing a discount, Amgen will be at risk financially if health plan member's cholesterol levels are not lowered enough. Harvard Pilgrim's deal with Amgen is one of the first to add a pay-for-performance element on top of the discount. But it's uncertain if this tactic will catch on, or if it will do anything to curtail high drug pricing. The retail price of a year's supply of

Repatha costs \$14,100, slightly less than the \$14,600 price tag of Praluent, the other major cholesterol drug approved by the FDA in 2015. Harvard Pilgrim did not negotiate any agreement for Praluent, which means Reptha will be on its preferred formulary (Herman, 2015).

In January 2015, the insurer also negotiated a discount on Gilead Science's Hepatitis C drug, Harvoni, in exchange for a preferred drug distinction. Although Harvoni was generally accepted as an excellent drug, curing Hepatitis C in many patients, the size of the patient population made the budget impact of the drug particularly problematic for many payers across the world. Given the numerous players in the Hepatitis C therapeutic area, competition enabled a number of innovative contracting deals to ease the net impact.

Dr. Josh Carlson and the Pharmaceutical Outcomes Research and Policy Program (PORPP) at the University of Washington initiated a program to identify and assess the use of "performance-based" reimbursement models for new medical products. Their Performance Based Risk Sharing (PBRS) web-enabled database is designed to be an up-to-date resource on performance-based risk sharing arrangements (also known as patient access schemes, market access agreements, and managed entry agreements, among others). The database includes detailed information about PBRS arrangements culled from publicly available sources and personal contacts. We define PBRsAs broadly as arrangements between a payer and a pharmaceutical, device, or diagnostic manufacturer where the price level and/or nature of reimbursement is related to the actual future performance of the product in either the research or 'real world' environment rather than the expected future performance (University of Washington, 2016). Table 2

(Appendix) shows a selection of publicly available Performance-Based Reimbursement Schemes.

### Assessment of Existing PBRsAs

Let us explore a number of publicly available PBRsAs and then discuss how such agreements could be implemented in a manner that specifically leverages the unique attributes of RNAi. The scheme between Proctor & Gamble, Sanofi-Aventis, and Health Alliance for the use of Risedronate in osteoporosis has its own unique aspects that differentiate it from other performance-based schemes. In this scheme, the two companies that jointly sell the osteoporosis drug agree to reimburse the insurer for the costs of treating non-spinal fractures suffered by patients who consistently take the medication. This appears to be the first published example of a manufacturer agreeing to cover the cost of disease-related sequela as opposed to discounting or refunding the cost of their product. This scheme lowers the medical costs to Health Alliance, considering hip and wrist fractures cost \$30,000 and \$6,000, respectively. This scheme further illustrates one of the proposed motivations for the implementation of performance-based schemes, decreasing the risk to the payer related to product uncertainty, in this case, the uncertainty about the benefits of Risedronate in terms of reducing nonspinal fractures (Carlson, 2010).

In May 2016, Cigna became the first insurer to reach value-based contracts for an entire new class of cholesterol drugs: Praluent, co-marketed by Sanofi and Regeneron Pharmaceuticals, and Amgen Inc.'s Repatha are the only two cholesterol-lowering drugs,

known as PCSK9 inhibitors, currently on the US market. Both drugs cost at least \$14,000 a year. If Cigna-insured patients who take the drugs are not able to reduce LDL cholesterol at least to the extent shown in clinical trials, the manufacturers will further discount the costs of the drugs, not just for patients who did not meet the cholesterol goals. If the drugs meet or exceed expectations, the original negotiated price stays, according to Cigna (Loftus, 2016).

Although PBRSA arrangements have the intrinsic appeal of tying reimbursement to a product's actual performance, there are significant barriers to their implementation. These include potentially high administration costs, lack of transparency, conflicts of interest, and whether health authorities will fund an appreciable proportion of a new drug's development costs (Adamski, 2010). Another challenge with innovative contracting strategies is determining the legality of the arrangement, and also determining the impact on government price-reporting ("best price"), which is required in the US in order for a manufacturer to be eligible to have its products covered by programs like Medicare and Medicaid. Additional concerns include the following: 1) limitations of current information systems in terms of tracking performance; 2) agreeing on the scheme details (e.g. the appropriate outcome measure or financial adjudication process); 3) physician push-back; 4) The "free-rider" problem, where other manufacturer or payer competitors may benefit from the information; 5) The lack of trust between payers and developers (Carlson, 2011). These obstacles continue to grow as products become more expensive. Finally many companies are also hesitant to engage in such arrangements because examples of successful arrangements are not widely available in the public domain- although that does not mean they do not exist.

## Potential for a New Pricing Opportunity for RNA Interference

Alnylam Pharmaceuticals, Inc. is developing innovative RNA interference (RNAi) therapeutics. RNA interference is a natural mechanism of gene silencing leveraged for therapeutic purposes. Small interfering RNAs (siRNA) target and silence messenger RNA (mRNA), preventing disease causing proteins from being produced (Figure 5). The process starts when double-stranded RNA is introduced into the cytoplasm, where it is cleaved into small interfering RNA (siRNA) by the enzyme Dicer. Alternatively, siRNA can be introduced directly into the cell. The siRNA is then incorporated into the RNA-induced Silencing Complex (RISC), resulting in cleavage of the sense strand of RNA by argonaute 2 (AGO2). The activated RISC-siRNA complex seeks out, binds to and degrades complementary mRNA, which leads to the silencing of the target gene. The activated RISC-siRNA complex can then be recycled for the destruction of identical mRNA targets (Whitehead, 2009).

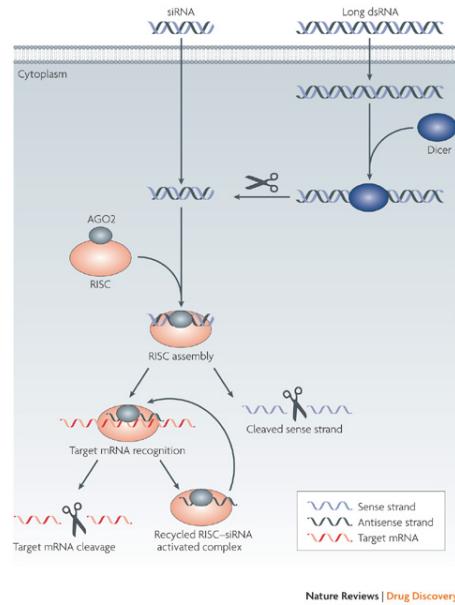


Figure 5. The Mechanism of RNA (Whitehead, 2009)

The effects of RNA interference are not permanent because the molecules target mRNA and not DNA. As a result, RNAi therapeutics must be administered periodically either intravenously or subcutaneously to have a sustained effect. RNAi is highly selective, with the ability to target virtually any protein. RNAi therapeutics would act upstream of where traditional therapeutics work, such as small molecules and monoclonal antibodies. RNAi therapeutics have been demonstrated to silence human disease genes in animal models (*in vivo*) and in several human clinical studies. Efficacy has been demonstrated by looking at target “knockdown.” Knockdown measures the reduction in translated protein levels as a percentage of baseline expression.

Due to this revolutionary biotechnology, Alnylam is uniquely poised take an industry leading position in establishing novel and innovative arrangements for pricing and reimbursement of RNAi therapeutics. In January 2015, the company launched its

2020 guidance for investors that reflects its expected transition from a late-stage clinical development company to a multi-product commercial-stage company with a sustainable development pipeline. The company is leading the translation of RNAi as a new class of innovative medicines. Alnylam's pipeline of investigational RNAi therapeutics is focused in 3 Strategic Therapeutic Area (STAr)s: Genetics Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare disease; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated liver-expressed disease targets for unmet needs in cardiovascular and metabolic disease; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics that address the major global health challenges of hepatic infectious diseases. In early 2015, Alnylam launched its' "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, Alnylam expects to achieve a company profile with 3-marketed products, 10 RNAi therapeutic clinical programs, including 4 in late stages of development- across its 3 STAr)s. The company's demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, Cubist, GlaxoSmithKline, Ascleptis, Monsanto, The Medicines Company, and Genzyme, a Sanofi company.



## Chapter III

### Methods and Analysis

The objective of this thesis is to establish a strong understanding of the US payer landscape and the particular dynamics at play in the US healthcare ecosystem. This investigation will also provide a foundational understanding of the payer perspective on novel RNAi therapeutics and how innovative, performance-based pricing structures can potentially drive payer coverage for such products, particularly in the context of orphan disease indications.

Through primary research with payers and experts in the field, as well as a literature review, we aimed to answer the following key questions:

1. What is the current payer environment for orphan drugs launched in US?
2. What drives willingness to pay for orphan products today and in the future?
3. What potential innovative structures could exist for siRNA therapies?

The project methodology employed primary, secondary, and case study research to gain an understanding of today's marketplace and to extrapolate on how the market could enable additional performance-based arrangements in the future. The analysis will drive to a set of recommendations that will best support emerging companies in the field of RNAi therapeutics as they consider implementing performance-based arrangements into their overall payer strategy.

It is also worth noting that each payer will require a tailored approach for each product, taking in to account the unique attributes of a given therapeutic indication. Each combination thereof (payer, manufacturer, product, indication) will need to be assessed individually to ensure a complete understanding of unmet needs, the value proposition that is potentially being offered and the optimal structure for innovative arrangements.

## Chapter IV

### Results

This section reports the results from our primary, secondary, and case study review, in the context of the following themes: Drug Reimbursement, Coverage Determination Process, Innovative Pricing Arrangements, Case Study Analyses, Opportunity for Innovative Pricing: Arrangements Evaluated.

#### Drug Reimbursement

Third-party administrators (TPAs) are prominent players in the health care industry and have the expertise and capability to administer all or a portion of the claims process between the providers and the payers. TPAs are normally contracted by a health insurer or self-insuring companies to administer services, including claims administration, premium collection, enrollment and other administrative activities. Payers may genuinely provide insurance where a company pays an insurance provider a given rate to take the risk on insuring employees' lives. A payer can also play the role of a TPA where they administer the health benefits, but take no risk. Most large corporations fully cover the actual expenses of their employees, while the TPAs charge a service fee, but do not assume actual risk.

Most payers manage medical and pharmacy coverage through separate TPA benefit programs: Pharmacy Benefit Reimbursement Management and Medical Benefit Reimbursement Management. Medical Benefit Management decision makers include

medical doctors, payer executives, and the Medical Policy and Technology Assessment Committee. This coverage typically includes physician visits, hospitalizations, surgeries, and medications that are infused or injected by a healthcare professional. Pharmacy Benefit Managers rely on medical doctors, pharmacists, payer executives, and the Pharmacy and Therapeutics Committee (P&T) for formulary insight, which is described in the next section. Pharmacy Benefit Management's scope of coverage includes oral medications and their formulary may be open (may cover unlisted drugs) or closed (only cover listed drugs, following an approval process). The drug formulary is updated with coverage decisions. Self-injected medications can be managed through either benefit program. As with many aspects of the industry, the above outline varies by payer and considerable variation exists across the country.

Payers utilize various mechanisms to manage reimbursement, with Medical Benefit Reimbursement utilizing deductibles, copays, co-insurance, and prior authorization. Pharmacy Benefit Management utilizes formularies, step therapy, prior authorization, and tiers. In recent years, many health plans have transferred drugs traditionally covered under the medical benefit to the pharmacy benefit in order to rein in costs and gain greater control over utilization. Comparisons are easier when medications are on the same benefit, as billing procedures, transparency and benefit structures are quite different across the medical versus pharmacy systems. National Drug Codes (NDC) are used to make and pay claims under the pharmacy benefit also allow for greater precision and sophistication when performing data analysis and utilization review.

Many payers outsource management of their pharmacy benefit to independent third party PBMs (Figure 6). PBMs have large numbers of clients ranging from large

national payers that have their own formularies to more regional payers and self-insured groups that typically defer to the PBM’s formulary design strategy. This was confirmed in an interview with a Director of Managed Markets, “Even if a regional payer has their own formulary, they’ll usually look to their PBM before they make their own decision.” Traditional payers face problems associated with increasing costs, specialized providers, and contracting leverage. The advantages of a specialized third party include the ability to: 1) focus on one type of benefit (not distracted by others); 2) employ administrative staff dedicated to one type of provider allowing streamlined billing for providers; 3) aggregate covered lives from several insurance companies, giving them more leverage in contract negotiations.







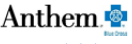




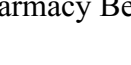

















						
Total Covered Lives	85MM	70MM	65MM	26MM	50MM	9MM
Lives on Primary Formulary	25MM	25MM	24MM	25MM	15MM	9MM
Example Clients*	     	    	    	 <ul style="list-style-type: none"> <li>• Alabama</li> <li>• North Carolina</li> <li>• Florida</li> <li>• Illinois</li> <li>• Kansas</li> <li>• Minnesota</li> <li>• Montana</li> <li>• Nebraska</li> <li>• North Dakota</li> <li>• New Mexico</li> <li>• Oklahoma</li> <li>• Texas</li> <li>• Wyoming</li> </ul>	    	

Figure 6. Pharmacy Benefit Manager Mapping (Health Advances Analysis)

## Coverage Determination Process

The primary research indicated payers are influenced by clinical considerations, social pressures, and system economics when deciding whether to cover a new therapeutic intervention. Clinical efficacy and safety are paramount in the approval decision for new products. The clinical factors include relative efficacy compared to the current standard of care, side effects, relative safety, and ease of use. Economic factors that impact coverage decisions may include financial burden(s) associated with a novel technology (confirmatory diagnosis required, administration costs, drug cost, monitoring, etc.) and the potential to save downstream costs (such as hospitalizations, organ transplant surgeries, other therapeutic interventions, etc.). Social factors may include disease severity, patient activism, technology hype, and patient cohort covered. From this standpoint, payers fear being portrayed negatively and losing members to competing plans to cover certain therapies. A variety of common diseases have strong advocacy groups behind them, but even some very rare diseases have strong social influence given the sophistication of their advocacy efforts. Indications such as hemophilia, Duchene's muscular dystrophy, and cystic fibrosis are highly influential, just to name a few. The coverage determination process also includes the clinical review of a new therapy, conducted by the P&T committee.

P&T committees are comprised of 10-25 independent clinicians. They are typically isolated from any information regarding pricing or contracting. The P&T committee review focuses strictly on clinical evidence supporting use of a new agent. KOLs provide input through this process; guidelines and published data are consulted as well. Agents ranked favorably by the P&T committee are subsequently reviewed by the

formulary review committee to determine terms of coverage (Leung, 2012). External parties are not regularly consulted at this point, however clinician input may be used to estimate demand. In formulary committee review, KOL and clinician input is used to estimate demand for a given product rather than assess clinical value. An internal committee, consisting of representatives from Industry Relations, Finance, Business Analytics, and Account Management, addresses the main question: What are the best business decisions given the ratings of the P&T committee? Clinical benefit and budget impact are the most important factors when designing a formulary although other factors can come into play as well.

The primary research through double blind interviews conducted at Alnylam Pharmaceuticals found that most of the time, RNAi therapeutics will follow a standard P&T and formulary review process, though economic considerations will be less important than the anticipated clinical benefit of these therapies. Payers consistently emphasized that patient outcomes are most relevant to contracting decisions in rare diseases, with one payer stating, “The bottom line is the outcome that you produce for the patient.” Another payer mentioned, “If we think two drugs for a rare disease produce similar clinical outcomes, we’ll never really try to make one preferred. It’s typically highly specialized doctors that treat these disease so we’ll usually just defer to their judgment on which to use.” Price sensitivity is limited given low prevalence of rare disease. One payer stated, “It’s not worth our time to negotiate for something that might be used in 10 our patients.” Another said, “Spend is measured by therapeutic area. Multiple Sclerosis (MS) is a single therapeutic area but orphan drugs is not so- orphans never really appear on our radar as a priority.” Payers anticipate using the same review

processes for novel RNAi therapeutics as they would for existing therapeutic modalities. “The efficacy of a new therapy is massively important, while the mechanism that results in that efficacy has little to no influence,” said one payer. Another payer agreed, “We’d expect to see the same type of clinical evidence for RNAi that we’d expect to see from anything else.”

In addition to payers, there are other organizations that influence coverage (Health Advances interviews and analysis). Payer contracting decisions are not typically influenced by competing payer decisions or patient advocacy organizations, although those organizations may influence coverage decisions. There have been recent decisions (ex. Hepatitis C with Viekira Park and Sovaldi/Harvoni) where large payers have seen what other large payers have done to contain costs within the space and they subsequently implemented contracts based on the competitive dynamics observed in the marketplace. One payer mentioned, “It’s very hard for us to not cover a drug that is generally covered by competitors. We look at competitors and know we’ll face pressure if they’re covering something we’re not.” Another payer offered, “Sometimes you don’t want to be the first to cover a new drug, especially if it’s much better than anything else in an indication with expensive patients. You may quickly find yourself with adverse selection and adverse retention problems.”

However, the secrecy surrounding most contracts limits the extent to which they can influence each other’s contract structures. “It’s hard to know what kind of contracts other payers are getting. It tends to be an advantage in negotiations if nobody knows what concession you’ve made in the past so there’s a ton of confidentiality around everything” admitted one payer. “We have some risk-sharing agreements in place but they’re not



public and we would need written consent from the drug companies to publicize them. They want to be able to get risk-free contracts where they still can,” remarked another payer. Patients and their advocacy organizations advocate for coverage but not any particular contract design. “As an insurance company, you never want to be on the front page of the newspaper for denying a patient some drug they need so if there’s an organized group getting behind something, you’ll be inclined to cover it.” Another payer said, “Patient advocacy groups care about patients being able to get a drug. They don’t care about the details of how you’ve contracted for it.” (Health Advances interviews and analysis).

### Innovative Pricing Arrangements

The information detailed in the background section (Chapter II) was echoed by our interviews, as innovative pricing arrangements (PBRsAs and cost caps) may be used to reduce budget impact and increase budget predictability, though required investment on the part of payers and manufacturers has limited widespread upfront implementation. Payers typically enter innovative pricing arrangements, beyond traditional discounting arrangements, to mitigate the risk posed by uncertainties around outcomes and/or budget impact at the time of launch and have little reason to implement such agreements if little uncertainty exists.

“When talking about PBRsAs, people are usually thinking about uncertainties that exist when the drug is launched because there isn’t enough data. I’m not sure

why you'd want to have that type of arrangement if the uncertainty has been cleared up.” – PBRSA Expert

“One of the hepatitis C manufacturers offered us an outcomes based risk-sharing agreement but there was no point. We know that over 95% of patients are going to be cured so it's not worth the effort it would take to do the arrangement” – Payer

PBRSA made public to date have centered around more prevalent indications (as opposed to orphan disease indications) because potential cost savings is more significant, especially given the fixed costs needed as upfront investments to implement such arrangements (Figure 7). PBRSA are rarely seen in orphan diseases, as budget impact is relatively low and administrative burden may be high. Rather, anticipated clinical outcomes and budget impact drive coverage decisions.

Interview feedback suggests that PBRSA for Repatha were made due to the potential for it to become more broadly indicated for patients with hypercholesterolemia which has an estimated US prevalence of ~75MM. However, United and Cigna have entered into PBRSA in the Hepatitis C space, suggesting that some payers may have underlying motivation to promote value-based care even if the arrangement has a negligible impact on their bottom line.

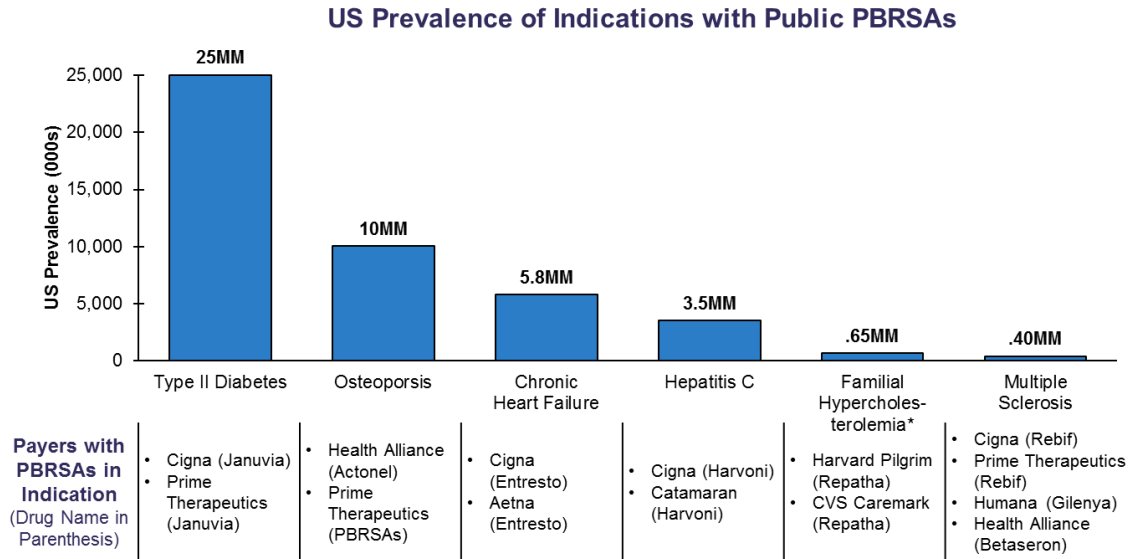


Figure 7. US Prevalence of Indications with Public PBRSA (Health Advances Analysis, CDC, AJMC, Datamonitor, Bui AL 2011, Wright NC 2014, Vishwanath R 2014)

### Case Study Analyses

By leveraging examples of PBRSA from others in the industry, we can learn more about the attributes that make the implementation of such arrangements most worthwhile. We can also see that manufacturers who engage in such arrangements may choose to be very public about their existence, though many agreements continue to be implemented in a highly confidential manner. Each case study assessed below highlights a set of particular drivers that led to a particular type of arrangement.

- Entresto in heart failure represents a structure designed to address uncertainty in costly outcomes.
- Ampyra in multiple sclerosis addresses clinical uncertainty, but leverages a free-trial approach differing from Entresto.

- Rebif in multiple sclerosis was designed to address payer’s uncertainty specifically around in patient adherence.
- Strimvelis in Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) eases annual budget impact while ensuring long-term efficacy.
- Premera Blue Cross is our payer-perspective case study. It focuses on applying more innovative methods to formulary design, where “high value” drugs are placed on the most favorable copayment tiers.

#### Scenario 1: Entresto Uncertainty in Costly Outcomes

The variability in the probability of a costly outcome (i.e. re-hospitalizations) is essential to the negotiation of a PBRSA, as demonstrated by Novartis’ agreement around Entresto. Entresto has a list price of \$4,560 per patient per year. It is administered in addition to existing drugs, meaning its costs add to existing cost burden. There are many Entresto-eligible patients with Chronic Heart Failure (CHF) in the US (Prevalence 5.8MM; Incidence: 550,000), contributing to a high risk of significant budget impact on pharmacy benefit. Uncertainty around outcomes is significant, as re-hospitalization is a common and expensive problem in CHF. Twenty-five percent of CHF patients are re-hospitalized, with each hospitalization costing \$13,000.

Entresto was shown to reduce hospitalization by 20% versus an ACE inhibitor alone, but it was not clear that this reduction would translate from a controlled trial to the real world. The reduction of readmissions is a particularly valuable metric for a hospital’s balance sheet. The Hospital Readmissions Reduction program, created under the ACA, initially evaluated how often patients treated for heat attack, heart failure, and pneumonia

had to return to the hospital within 30 days of discharge. Facilities with too high of a readmission rate saw their Medicare payments docked up to 1% in fiscal 2013 and 2% in the 2014 fiscal year. For the 2015 fiscal year, only 799 out of more than 3,400 hospitals subject to the program performed well enough on the 30-day readmission program to not face a penalty (Rice, 2015).

Given the size of the potential population and the uncertainty about translation into the real world, Novartis and two major US payers (Aetna and Cigna) struck noteworthy agreements to support the use of Entresto. Aetna and Cigna implemented PBRSA for Entresto based primarily on reductions in heart failure hospitalizations. Both agreements begin with a base rebate that is adjusted upwards or downwards depending on whether or not specific goals around reduced hospitalization are met. In both cases, the uncertainty as to whether the clinical trial results would translate into real world outcomes a common challenge that payers face was cited as the primary motivations for implementing the PBRSA when their existence was made public. Cigna's Press Release for Entresto PBRSA stated that competitive drug prices are important, but equally so is ensuring that customers' medications are actually working as well, or better than, expected.

As mentioned earlier, Harvard Pilgrim Health Care implemented a PBRSA for Entresto in June 2016. Entresto will be listed as a preferred therapy on Harvard Pilgrim's roster of medicines for which the company pays claims. This arrangement enables its customers to pay less out of pocket in co-pays than they would for rival drugs. Such performance-based contracts are part of an effort by health insurers and consumers to push back against rising prices for the prescription medicines that account for a growing

share of health care spending. Novartis also agreed to pay Harvard Pilgrim rebates if their treatment fails to meet certain performance measures. Specifically, Novartis agreed to refund money if Entresto does not reduce hospitalization for congestive heart failure by a certain undisclosed percentage. Entresto showed a 20 percent reduction in hospitalization compared with a different kind of heart failure drug in clinical trials. The contract protects the health plan and its customers if the drugs do not work as intended, but Harvard Pilgrim's Chief Medical Officer Michael Sherman said he would rather not receive any rebates. "What we'd like to see is more people moved from the drugs that aren't higher value to the drugs that are higher value," he said. "That reduces hospitalization, which is more important than the rebates. We don't want to go back and say your drug isn't working." (Weisman, 2016).

## Scenario 2: Uncertainty in Patient Adherence

EMD Serono's agreement for Rebif demonstrates adherence-based rebates may need to be incorporated into a more lucrative arrangement to capture the attention of payers. Rebif, approved in 2002, is a chronic therapy for multiple sclerosis (MS). Adherence to chronic therapies for a disease like MS, where patients are often asymptomatic for a period of time, is typically poor. Poor adherence results in reduced revenues for the manufacturer and also produces suboptimal clinical outcomes. If a patient does not seem to be adequately treated on Rebif, the patient would be more likely to switch to a different therapy. Therefore, incentivizing adherence with the proper dosing regimen would benefit the patient, the manufacturer, and the payer.

However, negotiating an adherence-based contract can be challenging and costly. An EMD Serono executive noted, “These contracts might seem simple but the devil is in the details. The definition of adherence alone is ten pages long.” Monitoring adherence can require building and implementing new systems. Improved adherence may lead to long-term benefits but can also lead to a short-term increase in drug spend. This is a dilemma, as commercial payers generally assume they will cover a patient for no more than three years.

In 2011-2012, Cigna and Prime Therapeutics implemented agreements where EMD Serono paid additional rebates if patients achieve specified levels of adherence to Rebif. The prospect of the rebates incentivized payers to ensure their Rebif patients are adhering to the medication. To further incentivize payers to implement an adherence-based contract, EMD Serono offered each payer outcomes guarantees related to cost containment. Cigna received additional rebates if its Rebif patients visited the ER or were re-hospitalized for MS relapses at a greater rate than they were in the year before the agreement was implemented (2010). Prime Therapeutics received additional rebates if the overall cost of care (including both pharmacy and medical costs) exceeded the cost of care for MS patients on other similar drugs.

Although information is available about the general structure of the agreement, little is known about its general success or failure.

### Scenario 3: Uncertainty in Responsive Patient Population

Ampyra (Acorda Therapeutics, Inc.; dalfampridine) is the first oral medication approved to improve a MS symptom. Approximately 87 percent of the estimated 400,000 MS patients in the USA have said they experience some limitation to their walking ability. Ampyra is prescribed to improve walking time and other motor activities by blocking potassium leakage from degenerated myelin sheath (the protective coating around nerve fibers). It is also thought to help aid in a hallmark characteristic of MS, by increasing nerve signal conduction from the brain to other parts of the body (Phillips, 2010). Ampyra was shown to be effective in 35-43% of individuals with MS in clinical trials via the twelve item walking scale (MSWS-12) (Acorda Therapeutics, 2011). Our recent primary interview with Tara Stevens, Senior Vice President of Trade Relations and Operations at Acorda confirmed this was an accurate range, with Ampyra shown to be effective in 47% of individuals with MS. It is important to note Ampyra is in addition to, rather than replacing, the expenses associated with branded MS biologics.

Although MS is a devastating and progressive disease, payers recognize that it must be managed to ensure cost-effectiveness. Patients with MS incur medical costs two to three times greater than those of all enrollees in a managed-care organization (Asche et al, 2010). Acorda offers a 60-Day Free Trial through their First Step Program, which allows patients to receive a free trial of Ampyra. The program allows patients to receive a 2 month supply if they meet the following criteria: cannot have filled an Ampyra prescription within the last 12 months, do not have any history of seizures and do not have moderate or severe kidney impairment, are not allergic to dalfampridine (the active ingredient in Ampyra), and are not a Medicare/Medicaid recipient. Patients must consult



a physician prior to receiving the free trial. Renewal criteria include documentation of at least a 20% improvement from baseline in timed walking speed or a stabilization or improvement of the baseline EDSS score (must be less than 7). The renewal dose of Ampyra will have the same restrictions as initial criteria (Prime Therapeutics, LLC ).

The 60-Day Free Trial is beneficial to all players in the healthcare system. It is designed so eligible MS patients can try Ampyra and determine if they respond before they or their health plans incur any expense for the drug (Acorda Therapeutics.com, 2016). This is a worthy approach, as it is easy to determine if a patient is responding and allows the time necessary to determine if they are responding to Ampyra. The average wholesale price for Ampyra, dosed 10mg twice daily was roughly \$1,056 per 30 day supply, or \$12,850 annually (Phillips, 2010). The company has raised the price several times since the drug was approved in 2010 to an annual cost of more than \$23,650 per patient. Acorda offers rebates and discounts off the list price that are likely to cut about 40% from the latest price increase. Ampyra generated \$351 million in sales for the first nine months of 2015 or 87% of total company revenue. Dr. Cohen, Acorda Therapeutics CEO said it took more than a decade to develop Ampyra and that the price hikes are “our way of insuring that we can survive and develop these programs and bring these new innovative drugs to market.” (MS Unites, 2016).

#### Scenario 4: Money-Back Guarantee

In August 2016, GlaxoSmithKline announced a money-back guarantee in Europe for its product Strimvelis, the first cure for a rare disorder to emerge from gene therapy. The treatment employs a virus to add a missing gene to the bone marrow of children with Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID), a sometimes fatal inability to fight infections. In a study involving eighteen children, carried out in Milan, all but three patients were cured of disease symptoms following Strimvelis administration.

According to Luca Pani, director general of the Italian Medicines Agency (AIFA), which set the price and terms during negotiations, “If it does not work, they will return the money.” GSK bought the rights to the treatment in 2010 and won approval earlier this year to sell it in Europe but because of its complexity the company will offer it only in Milan, requiring families to travel and spend weeks there. That means the Italian price will apply to all of Europe. The Italian agency is unusual in that it already imposes pay-for-performance rules on some cancer drugs. It maintains that 135 patient registries to track how well they work and Pani says Italy has collected more than 250 million euros in refunds. It is estimated that GSK might end up refunding one in six treatments.

Strimvelis is one of the most expensive one-time treatments ever sold by a drug firm at \$665,000 (Regalado, 2016). This raises the question: Are gene-therapy drugs the most expensive in history or one of medicine’s greatest bargains? Strimvelis’ price is seen as a bargain to some, as the cost of a bone marrow transplant from another person can reach \$1million or enzyme injections that cost \$250,000 a year. The expense of these drugs and the care needed for a sick child can quickly add up to millions. According to

Pani, GSK approached that Italian agency with a price “nearly double” what was eventually settled on. “It’s really difficult, because everyone’s economic models involve regular drugs and these are not regular drugs...it’s a symbol of the future,” said Pani. The pricing of Strimvelis is important as potential cures for hemophilia, blindness, and metachromatic leukodystrophy could reach the market next and be similarly expensive.

The big question is not whether gene therapy costs too much- it’s whether companies can make any money at it, especially treating ultra-rare diseases. Only about a dozen children are born with ADA-SCID annually in Europe, generating \$8 million in revenue. This amount is a blip to companies like GSK that sell \$30 billion worth of drugs each year. Dr. Phil Reilly, Third Rock Venture partner, states “we need a new model for ultra-rare disorders, because we are going to develop these treatments.” Reilly believes money-back guarantees and pay-as-you-go schemes are two ways to make high sticker prices palatable. GSK admits it will not make much money off Strimvelis and sees the treatment as a way to help patients and gain experience with treatments involving genes and cells. GSK hopes Strimvelis will be the first of a number of innovative gene-therapy medicines that they will bring to patients and believes the industry will need to adapt the way in which medicines are priced and funded.

This payment structure addresses some of the key hurdles that the implementation of payment for a cure must overcome. For example, even for a small patient population, incurring such high expenses for one patient in one calendar year is considered catastrophic. By paying over time, payers are able to better stay within their annual budgetary constraints. Furthermore, long-term follow-up in the real world is not available at the time of launch. Since the actual value of the therapy cannot be certain initially, this

type of performance guarantee provides payers with the reassurance that should the long-term outcomes not be achieved, the risk will be transferred back to the manufacturer.

#### Scenario 5: Value-Based Insurance Design

The rise of cost-sharing in prescription drug plans has shifted a larger proportion of costs onto plan members. Value-based insurance design attempts to align drug copayment tier with value of each therapy, rather than its cost. Historically, formulary design has been structured such that lower out of pocket copayments were required when patients purchased low-priced generic drugs and higher out of pocket copayments were required when patients purchased high-priced branded drugs. However, this design has not resulted in the intended effect of deterring patients from the higher priced agents.

Thus, in 2010, Premera Blue Cross, a large not-for-profit health plan in the Pacific Northwest, implemented a value-based drug formulary (VBF) pilot that explicitly uses cost-effectiveness analyses (CEA) after safety and efficacy reviews to estimate the value of each individual drug (Sullivan, 2015). The CEA compares the relative value of one therapy with a reference standard therapy using an incremental cost-effectiveness ratio (ICER) (Weinstein, 2009). When comparing two drugs, the ICER quantifies the incremental cost required to obtain an additional unit of health outcome (e.g. quality-adjusted life-year). An external panel of clinical, economic, and bioethical experts and lay members use the ICER estimates along with information on additional social or ethical values to assign the drug to the appropriate copayment tier. Drugs with higher ICERs are placed on higher copayment tiers to disincentivize use and drugs with lower ICERs are placed on lower copayment tiers to incentivize greater use and compliance

(Yeung, 2016). ICERs are typically used as an evaluation tool in many European countries but they are not yet widespread in US practice.

For Premera, the VBF and copayment changes enabled pharmacy plan cost savings without negatively affecting utilization in key disease states. There was a 10% or \$8 per member per month reduction in overall medication expenditure in the test cohort of patients who received treatment via the VBF design versus the control cohort of patients who continued to receive their treatments with the traditional formulary/copayment structure. The medication savings equals \$1.1 million for the cohort over the 3-year post policy time frame. For medications moved into lower copayment tiers, mean copayments decreased from \$14 to \$7. For medications moved into higher copayment tiers, mean copayments increased from \$40 to \$79. In the context of overall copayment increases, member cost sharing increased less for members with chronic illness (ex. diabetes, hypertension, and dyslipidemia) than was projected, without negatively impacting adherence.

This suggests that the VBF and the preventative drug tier may incentivize greater adherence by reducing the out of pocket costs for patients. The tiered approach has the advantage of being less restrictive, while still promoting the use of higher-value products. The study demonstrated that a VBF will be well-received in settings where a trust relationship exists between an employer and associates, such that most associates believe that the employer is acting in their best interest. Limitations of the VBF include:

1. Timely access to high quality economic evidence from pharmaceutical manufacturers or third party assessments,
2. Uncertainty of VBF impact on actual health outcomes,




3. Selecting only a working age population, unobserved confounding (Yeung, 2016).

### Opportunity for Innovative Pricing: Arrangements Evaluated

Similar to these case studies, the implementation of innovative pricing arrangements to mitigate potential sources of uncertainty such as response to therapy, dosing, and utilization may also be implemented in the field of orphan diseases (Table 3).

Table 3. Sources of Uncertainty and Innovative Arrangements

(Health Advances Interviews)




Potential Sources of Uncertainty		Solution
<p><i>Response to Therapy</i></p> <ul style="list-style-type: none"> <li>• Payer concerned that drug may not produce desirable outcomes (either efficacy or safety) in many of the patients who may take the drug               <ul style="list-style-type: none"> <li>– Ideal when the endpoint in pivotal trials was a surrogate like LDL reduction</li> </ul> </li> </ul>		<i>PBRSA</i>
<p><i>Dosing</i></p> <ul style="list-style-type: none"> <li>• Payer concerned that patients may be administered larger doses than indicated resulting in greater plan spend               <ul style="list-style-type: none"> <li>– This concern is particularly acute for infused therapies</li> </ul> </li> </ul>		<i>Patient Cost Cap</i>
<p><i>Utilization</i></p> <ul style="list-style-type: none"> <li>• Payer concerned that a larger number of patients than anticipated may take the drug either through off-label use or through adverse selection of plan</li> </ul>		<i>Price-Volume Agreement with Cap</i>

Three types of innovative pricing arrangements were identified and evaluated for potential implementation in the field of rare orphan indications where RNAi therapeutics may be applied (Table 4. Health Advances interviews and analysis): 1. Performance-Based Risk-Sharing Agreement (PBRSA) with two approaches depending on outcomes achieved in clinical practice.

2. Patient Cost Cap, where payment is based on per-patient stipend and the annual cost per patient does not exceed a given threshold.

3. Portfolio Price-Volume Agreement with Cap, where payment arrangement is based on total spend across a portfolio of therapies.

Table 4. Potential Innovative Pricing Schemes Descriptions for RNAi Therapy  
(Health Advances Interviews)

<p style="text-align: center;"><b>PBRSA</b></p> 	<ul style="list-style-type: none"> <li>• Payment arrangement based on outcomes achieved in clinical practice</li> </ul> <p><i>Approach 1:</i></p> <ul style="list-style-type: none"> <li>• Treatment initiation free of charge, followed by assessment of knockdown</li> <li>• Level of knockdown needs to exceed a pre-specified amount for the payer to reimburse for subsequent treatment</li> </ul> <p><i>Approach 2:</i></p> <ul style="list-style-type: none"> <li>• Treatment is reimbursed by payer from the start</li> <li>• After a period of time, the efficacy of the drug is evaluated using pre-specified endpoints (e.g. reductions in hospitalizations)</li> <li>• If patients do not see an improvement in the pre-specified criteria, the manufacturer refunds some or all of the cost of therapy to the payer</li> </ul>
<p style="text-align: center;"><b>Patient Cost Cap</b></p> 	<ul style="list-style-type: none"> <li>• Payment arrangement based on per-patient spend</li> <li>• The payer pays no more than a pre-determined amount over a defined period of time (e.g., 2 years) for a patient on an RNAi therapeutic</li> <li>• Once the cost cap is reached, the therapeutic is provided to the patient at no or very low cost for the remainder of the set amount of time</li> </ul>
<p style="text-align: center;"><b>Portfolio Price-Volume Agreement with Cap</b></p> 	<ul style="list-style-type: none"> <li>• Payment arrangement based on total spend across a portfolio of therapies</li> <li>• Assumes a manufacturer has several (~5) different RNA interference therapeutics in development for multiple orphan indications</li> <li>• The payer pays no more than a pre-determined amount over a defined period of time (ex. 2 years) for all patients on these RNAi therapeutics</li> </ul>

The results of double blind discussions with payers suggest that the potential for a patient cost cap arrangement is significant, as it would require relatively low investment by both the payer organization and the manufacturer. Payers were highly interested in this arrangement given questions around dosing for an RNAi therapeutic. One PBRSA expert asked, “Dosing is the biggest source of uncertainty I see here. If a patient shows 70% knockdown, do you give them larger doses to try to get to 90%? That means drug costs

could balloon fast if you pay on a mg/kg basis.” With the exception of understanding extent of dose variability (variability in quantity or frequency), there would be limited investment required, as tracking patient expenditures is feasible with existing data collection capabilities. Note: the clinically meaningful answer to the payer’s assumptions here are not yet understood as pivotal clinical studies for RNAi therapies are ongoing at the time of this writing

It’s important to note offering innovative contracting terms when negotiating versus a competitor may not always be advantageous. Risk-sharing arrangements are not a substitute for traditional rebates and result in greater concessions from manufacturers. As one industry executive states, “you don’t get goodwill from a payer by offering them a risk sharing agreement. You get goodwill by offering them a drug at the right price in the first place.” Most existing risk-sharing agreements, such as those for Entresto and Rebif, are structured as additional outcomes-based rebates on top of traditional rebates rather than outcomes-based rebates given in lieu of traditional rebates.

Payers may simply use the offer of a risk-sharing agreement to extract greater concessions from competitors. “If somebody offers me a risk-sharing agreement, I’ll often try to see if who they are bidding against will do the same thing so I can get an even bigger rebate either with or without the agreement,” said one payer. Even if a manufacturer can win preferred placement or exclusivity through an innovative contracting arrangement, they risk reducing long-term revenues by triggering a price war. “You have to play chess not checkers. These contracts have a defined length, sometimes as little as a year, and if you knock a competitor off a formulary, they’re going to spend



that time devising the sweetest deal they can in order to get back on,” offered one industry expert.

Innovative pricing arrangements can foster goodwill for manufacturers in our current era of increased scrutiny on pharmaceutical pricing. However, there are barriers to implementation: cost or resources required for payer to implement, bystander effect—many payers are unfamiliar with these arrangements and wait for others to implement them, reluctance from manufacturers to pay for patient failure, disagreement between payer and manufacturers to pay for patient failure, and disagreement between payer and manufacturer on measures of “performance.” Negotiations required to reach consensus on measures of “performance” often extend the coverage review process, discouraging manufacturers from entering such discussions. These arrangements do not obviate the need for rebates from a manufacturer but can help “sweeten the deal.” Mark Bertolini, Aetna Chairman and CEO, describes the situation as the following: “It’s inning number one (in terms of value-based pricing for drugs) because just talking about outcomes is an amorphous conversation. The conversation with pharma that we’re having needs to be much more specific.”

### Payer Prioritization

For emerging companies, particularly those in the orphan disease space with a novel mechanism of action and a deep portfolio, an exercise in payer prioritization may help streamline the use of internal resources for awareness and educational activities. It

may also help in understanding which potential payers may be more interested in a pilot program to assess the feasibility of novel arrangements in this context.

Payers that already manage against budget impact, have significant resources and infrastructure, and have demonstrated a willingness to be innovative in the past, will potentially be most receptive to an innovative pricing arrangement for RNAi. Our exercise started with a set of 34 payer organization, selected on the basis of total covered lives and pay type to ensure adequate representation of commercial payers, IDNs, PBMs, and government organizations. The relevant metrics were chosen based on feedback gathered during payer and PBRSA expert interviews: Numbered of Covered Lives, Size of Excluded Drugs List, Degree of Orphan Management, Number of Publicized PBRsAs and Payer Type.

1. Number of Covered Lives: Larger plans are likely to have higher number of patients suffering from a given orphan disease. Larger plans may also be likely to influence the decision of smaller plans.
2. Size of Excluded Drugs List: Payers with larger lists may be more inclined to negotiate for drugs indicated for conditions that affect a small number of their patients. This is a proxy for how closely the payer manages their drug spending.
3. Degree of Orphan Drug Management: Some plans give certain drugs better formulary placement or require step edits in orphan indications where there are more than one approved agent. These decisions may reflect a willingness to negotiate contracts in orphan indications.











4. Number of Publicized PBRsAs: Payers that have implemented PBRsAs will not need to be convinced of their value and will likely be willing to make more. Payers that have publicized PBRsAs may also see value in any positive press that comes from announcing these arrangements.

5. Payer Type: Preliminary feedback indicates lack of infrastructure to measure patient outcomes can be a significant barrier to PBRSA implementation. INDs already have most of the requisite infrastructure in place, thereby reducing the import of this barrier for them. Most PBM clients (who utilize the PBM formulary) do not have adequate data collection capabilities. In addition, it is challenging for PBMs themselves to track outcomes, as they are working with a number of different plans.

United, Anthem, Cigna, and Aetna are the largest commercial payers, however their interest in performance-based agreements may be limited given that only one such agreement has been made public across all three players (Table 5). Given their size, they are most likely to have a higher number of patients suffering from a given orphan disease. In indications where more than one therapeutic alternative exists, payers may place certain drugs on an excluded list to prevent utilization if an alternative therapy is deemed similarly efficacious. The increasing budgetary pressures are even driving management of therapeutic options within categories that were historically unmanaged, such as orphan disease indications.











Through assessing the historical behavior of key US payers, one can gauge which payers may be open to discussing performance-based arrangements for emerging RNAi therapeutics.

Table 5. Example of Potential Payer Prioritization

Rank	Payer	Payer Type	Lives Covered (MM)	Number of PBRsAs	Degree of Orphan Drug Management	Size of Excluded Drugs List
1		Commercial	21.8	1 (Public)	Moderate	100
2		Commercial	58.5	None public	High	66
3		Commercial	38.7	None public	Low	N/A
4		Commercial	7.5	4 (Public)	Moderate	38
5		PBM	70.0*	1 (Public)	Low	124
6		PBM	25.0*	3 (Public)	Low	N/A
7		PBM	65.0*	1 (Public)	Low	64
8		Commercial	13.8	1 (Public)	Moderate	N/A
9		PBM	85.0*	None public	Low	80
10		IDN	10.1	Several (Private)	Low	N/A

One example of an orphan indication where utilization management is significant is the field of Hereditary Angioedema (HAE). In HAE, there is one prophylactic treatment on the market to prevent the characteristic swellings that are extremely burdensome for patients. Four rescue therapies are also on the market for on-demand treatment when an attack occurs. As illustrated in Table 6, each payer takes a different approach to formulary design for these therapies.

Table 6. Degree of Orphan Drug Management: Hereditary Angioedema

Payer	Coverage Guidelines	Formulary <sup>1</sup>	Kalbitor	Berinert	Firazyr	Ruconest	Cinryze <sup>2</sup>
	No step edits required	UnitedHealthcare Advantage (3-Tier)	Medical	Tier 2 (PA)	Tier 3 (PA)	Not Listed	Medical
	No step edits required	Aetna Premier 5-Tier Open	Tier 5 (PA)	Tier 5 (PA)	Tier 4 (PA)	Tier 5 (PA)	Tier 4 (PA)
	No step edits required	Cigna Legacy 3-Tier	Medical	Medical	Tier 3 (PA)	Not Listed	Medical
	No step edits required	Anthem BCBS (3-Tier)	Tier 3 (PA)	Tier 3 (PA)	Tier 3 (PA)	Tier 3 (PA)	Tier 3 (PA)
	No step edits required	Humana Rx4 Traditional	Medical	Medical	Tier 4 (PA)	Medical	Medical
<i>Background Information</i>							
<i>Manufacturer</i>							
<i>Indication</i>			Acute HAE Attacks	Acute HAE Attacks <sup>3</sup>	Acute HAE Attack	Acute HAE Attacks	HAE Prophylaxis
<i>ROA</i>			SC by HCP only	IV	SC	IV	IV
<i>Year of Approval</i>			2009	2009	2011	2014	2008

While integrated systems are more likely to have the interest and capabilities to implement novel pricing models, even the largest Integrated Delivery Networks (IDN) represent a small fraction of total covered lives (**Error! Reference source not found.**Figure 8). An IDN is a formal system of providers and sites of care that provides both health care services and a health insurance plan to patients in a particular geographic area. IDNs may be more motivated to implement innovative contracts especially those centered on longer term outcomes.

“Just by being an IDN, there’s already a degree of innovativeness, so I’d imagine they’d be willing to push the envelope a little further.” IDNs make great targets for outcomes based agreements since they tend to hold onto patients longer than commercial payers. As a result, they’re much more interested in things that could happen 5-10 years down the line like transplants. IDNs have substantially lower

infrastructural barriers to implementing outcomes based arrangements than other types of payers.” –Industry Expert

Another IDN payer commented, “these types of arrangements are relatively straightforward for us to setup. We have all the patient’s electronic medical records and everything is flowing through something that’s already part of our systems.”

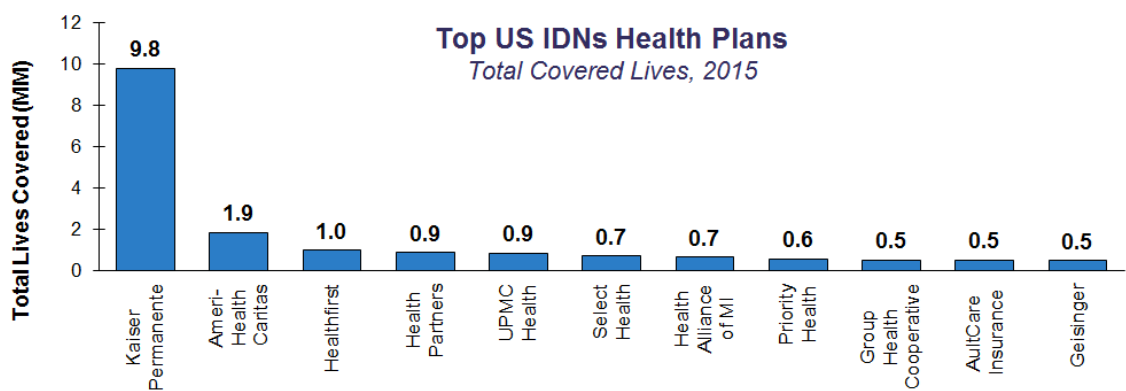


Figure 8. Top US IDNs Health Plans, Total Covered Lives, 2015

(AIS Directory of Health Plans 2015)

The other payer types in consideration are PBMs. Though accounting for a substantial number of lives (Figure 9), most PBMs do not represent attractive early targets for negotiating innovative contracting arrangements. PBMs are not responsible for a plan’s medical benefit, reducing their incentive and capability to structure contracts based on medical cost-offsets. PBM profitability may largely depend on achieving the

largest “spread” between the rebates and innovative contracts. Infrastructure barriers may be especially significant for independent PBMs as they may have a vast number of clients, each of whom administer their pharmacy benefit separately.

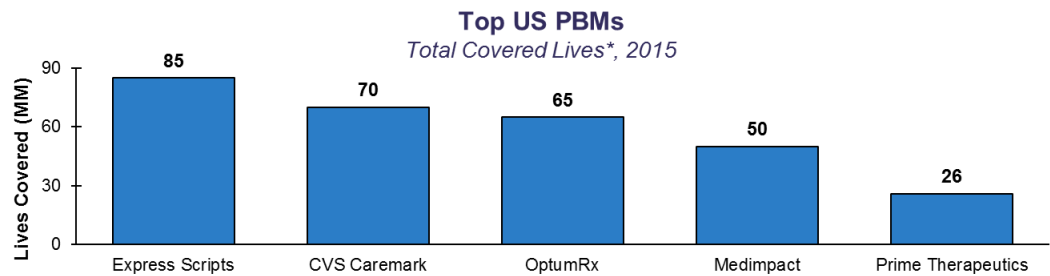











Figure 9. Top US PBMs Health Plans, Total Covered Lives, 2015

(AIS Directory of Health Plans 2015)

Based on the few PBSRAs made public, Cigna, Humana, and Prime Therapeutics appear to be the most willing to implement performance-based risk sharing agreements (Table 7.)

Table 7. Publicized PBRsAs

Payer	Number of PBRsAs		Details		
	Publicly Announced	Additional Information	Year	Manufacturer	Drug Name
 Cigna	4	May not be representative of likelihood to enter PBRsAs relative to other payers but rather a greater propensity to publicize these arrangements	2016	Novartis	Entresto
			2015	Gilead	Harvoni
			2011	EMD Serono	Rebif
			2009	Merck	Januvia and Janumet
 Humana	1	Press releases suggest a total of 13 arrangements have been made	2015	Novartis	Gilenva
			2012	EMD Serono	Rebif
 PRIME THERAPEUTICS	3	Through their CareCentered program	2011	Merck	Actonel
			2011	Warner Chilcott	Januvia
			2011	Warner Chilcott	Januvia
 aetna	1	Interview feedback suggests >1	2016	Novartis	Entresto
 Harvard Pilgrim HealthCare	1	-	2015	Amgen	Repatha
 CVS CAREMARK	1	-	2015	Amgen	Repatha
 catamaran	1	-	2015	Gilead	Harvoni
 OPTUMRx	1	-	2015	Gilead	Harvoni
 Health Alliance	1	-	2009	Sanofi	Actonel

## Chapter V

### Discussion

This section describes the results in a “big picture” perspective and provides recommendations to the company for market access work moving forward. Case study limitations are also included in this section.

#### Case Study Recommendations for RNAi Therapeutics

Given limited price sensitivity for orphan disease therapies, any promising performance-based agreements would likely prioritize simplicity over novelty. Companies interested in crafting a US payer strategy to include formulation of these arrangements will be met with great resistance if the structure of the arrangement or arbitration thereof is overly complex. Rare diseases with high societal and financial burdens may have the most potential for such performance-based arrangements,



particularly if multiple therapies are set to enter the market and enable competition across multiple therapies. Each arrangement would need to be tailored for the given patient population and unique attributes of the therapeutic indication.

In rare diseases, payers are likely to consult KOLs to assess clinical value and estimate demand. Payers will evaluate RNAi therapeutics in the same manner as other rare disease therapies- on the basis of meaningful clinical impact. Cost-effectiveness ratings- while gaining the attention of US payers, are not factored into contracting decisions, since clinical and economic impact are evaluated separately by most plans. Note, in some European countries, a specific cost-effectiveness threshold is implemented and strictly used in determining pricing and reimbursement assessments. Patient advocacy organizations and decisions made by other payers may influence coverage decisions, but rare disease therapies are typically not at risk of exclusion from formularies.

Financial-based arrangements, such as capitated payment schemes, (e.g. cost cap per patient) should be evaluated for indications with significant variability in dosing or utilization as a way to address uncertainty. Offering a payer a means by which to increase budgetary predictability, and potentially avoid catastrophic expenses or significant budget deviations, may allow for quicker acceptance than novel PBRsAs.

Should the concept of PBRsAs have potential specifically in the field of RNAi therapeutics, it will be advantageous to correlate knockdown of the target protein with meaningful clinical outcomes on a product by product basis. Additionally, structuring a PBRSA around a given endpoint, reduction in liver transplants for TTR amyloidosis for example, may be viable given difficulty evaluating this endpoint in clinical trials

(creating uncertainty) and the cost of the procedure to payers. However, proposing a PBRSA can backfire if payers perceive that actual risk to the manufacturer is low and that the PBRSA is a tactic to obtain market access without offering attractive rebates.

Some US payers closely manage budget impact, have significant resources and are investing in advanced infrastructure. They have demonstrated a willingness to be innovative with performance-based arrangements and may be particularly receptive to early discussions regarding RNAi therapeutics. United Healthcare and Aetna for example are ideal early targets, based on their high degree of orphan drug management and monitoring capabilities.

Given the complex nature of the US healthcare system, payers are not the only stakeholder with whom emerging manufacturers need to engage. When assessing the feasibility of a proposed contracting arrangement, US payers do not generally look outside their organizations, thus external organizations typically do not directly influence payers' coverage or contracting decisions. In rare disease, however, payers are likely to consult KOLs to assess clinical value and estimate demand. Patient advocacy groups, specific to a given disease or more general bodies, could also generally influence highly specialized therapeutics.

The Medical Affairs function, including its team of field-based Medical Science Liaisons (MSLs), healthcare professionals with advanced scientific training and academic credentials, will also be a vital component to a successful payer strategy. MSLs will be needed to not only explain a novel mechanism of action such as RNAi, but they may also support the development of relationships with clinical KOLs to help ensure a strong alignment between physician and patient needs and the data delivered in the clinical

studies. KOLs may be influential in formulary committee review and adoption of new therapies so their experience with RNAi therapeutics in the investigational stage will be key. MSLs are also becoming more important in the education of payers since a strong clinical orientation will be required to explain the benefits of RNAi therapeutics.

### The Healthcare System

The implementation of a broad performance-based pricing scheme is a gratuitously complicated project (Dobson, 2016). In an ideal world, three things must line up for it to work:

- 1) Consensus that a single care pathway is superior to all others;
- 2) A mechanism to enforce the use of that optimal approach;
- 3) A way to measure the direct impact of an intervention (ex. a patient taking a drug for a given period of time).

The challenge of aligning those three necessities is the primary reason why outcomes-based pricing, regarding indication-based reimbursement within certain categories, has not evolved as quickly as many in the industry would like. It does not help that the healthcare system remains “a work in progress.” What we have, in terms of infrastructure, isn't sophisticated enough,” says EY partner Susan Garfield, co-author of the consultancy's recent report *A Road Map to Strategic Drug Pricing*. She points to any number of small issues that, collectively, have contributed to delays. “You need data systems that can talk to each other. You need tools to help stakeholders come together to share information that documents the impact of different therapies and processes. You

need incentives to drive collaboration.” How long will evaluation periods for outcome measurement last? What data will be needed, where will it be housed, and who will have access to it? Practical realities are impeding progress at least as much as philosophical and financial ones.

Garfield believes healthcare stakeholders need to depart from what she calls “the land of 1,000 pilots” and start scaling up those programs and systems that show the most promise. “A lot of people are investing effort into finding a simple measure to show outcome or impact, but the future is going to be more complex,” she explains. “There's not going to be a binary yes, this worked or no, this didn't work.”

Dr. Steven Miller, Express Scripts' Chief Medical Officer, agrees with the gist of Garfield's assessment:

“Right now, the systems are just not mature enough to use outcomes as the basis for reimbursement. We're building capacity to get there eventually. Those enhanced systems will need to truly demonstrate in the real world how valuable, or lacking in value, some products are. Our relationship with pharma is more substantial than it's ever been...Everybody wants sustainability in the marketplace, whether through outcomes or indication-based reimbursement in oncology or something we don't know yet. It doesn't mean we'll always be on the same page, but we're constantly in dialogue and that's a good place to be.”

(Dobrow, 2016)

There's no shortage of creative thinking about ways to nudge the industry forward. Dr. Françoise Simon, professor emerita at Columbia University and senior faculty at Mount Sinai School of Medicine, points to a system soon to be introduced in a

handful of European countries that places a premium on the most innovative products. She explains, “It's kind of an innovation rating on a scale of one to five...makers of products that rate high for innovation are going to be allowed to negotiate a premium price. Me-too products are not going to be reimbursed.” This would be ideal for innovative manufacturers such as those in the RNAi space. As it currently stands however, the novelty of a drug’s mechanism of action does not matter to formulary reviews with US payers.

Our historical pricing model, which is built on unit-based pricing, is too one-dimensional for the marketplace’s current needs. It has resulted in incentives that encourage biopharma companies to make pricing decisions that are driven by what is possible rather than what other stakeholders consider reasonable, creating conflict. In this environment, there is a real risk that payers will use blunt methods to curb costs, constraining revenue growth for the biopharmaceutical industry. With multiple therapeutic options available in almost every drug class, a majority of products now coming to market will be classified as having “potential value” until there is proven evidence. As a result, at launch, many products must bridge an evidentiary “value gap.” Because of their high price tags, this value gap is especially pronounced for specialty medicines (Garfield, 2016).

### Case Study Limitations

The special features of case study research that provide the rationale for a given case study’s selection also present certain limitations. Qualitative case studies are limited by the sensitivity and integrity of the investigator, considering the researcher is the

primary instrument of data collection and analysis. An unethical case writer can select to include and exclude data to reach a specific, predetermined study outcome. Therefore, evaluators of case studies and the authors themselves need to be aware of biases that can affect the final product (Marriam, 2009). Hamel observes, "The case study has basically been faulted for its lack of representativeness...and its lack of rigor in the collection, construction, and analysis of the empirical materials that give rise to this study. This lack of rigor is linked to the problem of bias...introduced by the subjectivity of the researcher and others involved in the case (Hamel, 1993)."

Further limitations involve the issues of reliability, validity, and generalizability across both primary and secondary research. Interviewee responses are subject to the common problems of bias, poor recall, and inaccurate articulation (Yin, 2009). The scope of the payer discussion guide may also be either too general or does not cover the right criteria, prompting alterations to the questionnaire. We acknowledge that we could have been declined interviews with thought-leaders, impeding data collection and analysis. We also acknowledge this investigation is a preliminary step in learning about the landscape in preparation for an anticipated product launch of an RNAi therapeutic. Clinical considerations, social pressures, and system economics all influence the decision to cover a new technology. The interviewee's familiarity or bias with the new technology may be variable.

## Chapter VI

### Conclusions

Biopharmaceutical companies are an incredible source of American innovation and revolutionary treatments for debilitating diseases. Commitment to this innovation is of great importance in cases of orphan diseases, where life-saving medical expenditures are the only disease-modifying or curative, but come at high costs. The US is about to radically change how it pays for healthcare. Unit-based pricing arrangements have historically been the standard way the US pays for prescription drugs or physician services. In order to address uncertainty around outcomes, dosing, or utilization and the associated costs, certain US payers have entered into innovative pricing arrangements. Based on the assessment conducted herein, value-based innovative pricing arrangements, do have significant potential for use in orphan disease indications for RNAi therapeutics.

In the September 2016 *Forbes* article, “Don’t Let Epipen Threaten Innovation,” several biotech CEOs, including Alnylam CEO John Maragonare, offered their opinion for what is needed to combat escalating drug prices:

“Our healthcare system needs both innovators and generics to operate efficiently. The generics industry exists to provide a competitive marketplace for older drugs, (whose patents and/or other exclusivity have expired) at reduced prices. Roughly 90% of all drugs today are generics. A strong, competitive generics industry supports drug innovation. When multiple generic versions of a medicine are available, this serves to lower the cost of medicines after innovator companies

have received a fair return for the enormous risk and investment in research and development of new therapies.”

The generic market can operate successfully, as biotech has the largest community of investors (individuals, venture capitalists, and mutual funds) who are willing to invest in this high-risk work, despite that only 10% of drugs entering clinical studies will be approved. The biotech industry invests close to 20% of its revenue in research and development, more than any other industry. In 2015, this equated to more than four times the research and development investment of the NIH. Biotech CEOs believe we need fixes to the current system for getting generic competitors to market, once the innovator drug’s exclusivity period has expired. The Epipen episode would not have occurred in the presence of robust generic competition and there are policies that could accelerate the ability of generics companies to come to market with cheap copies of older drugs (Cohen et al, 2016).

Drug pricing issues involve not just drug companies but a number of entities such as PBMs, insurance companies, wholesalers, pharmacy chains and hospitals. Each player must secure a portion of the profit in the value chain, which contributes to driving up the gross price of prescription drugs. We need all of these stakeholders at the table, along with patient groups, doctors, regulators, and other segments of the healthcare industry to creatively discuss a framework that will ensure affordable medicines, while not curtailing the incentive to discover and develop extraordinary advances that we all want and urgently need.



# Appendix

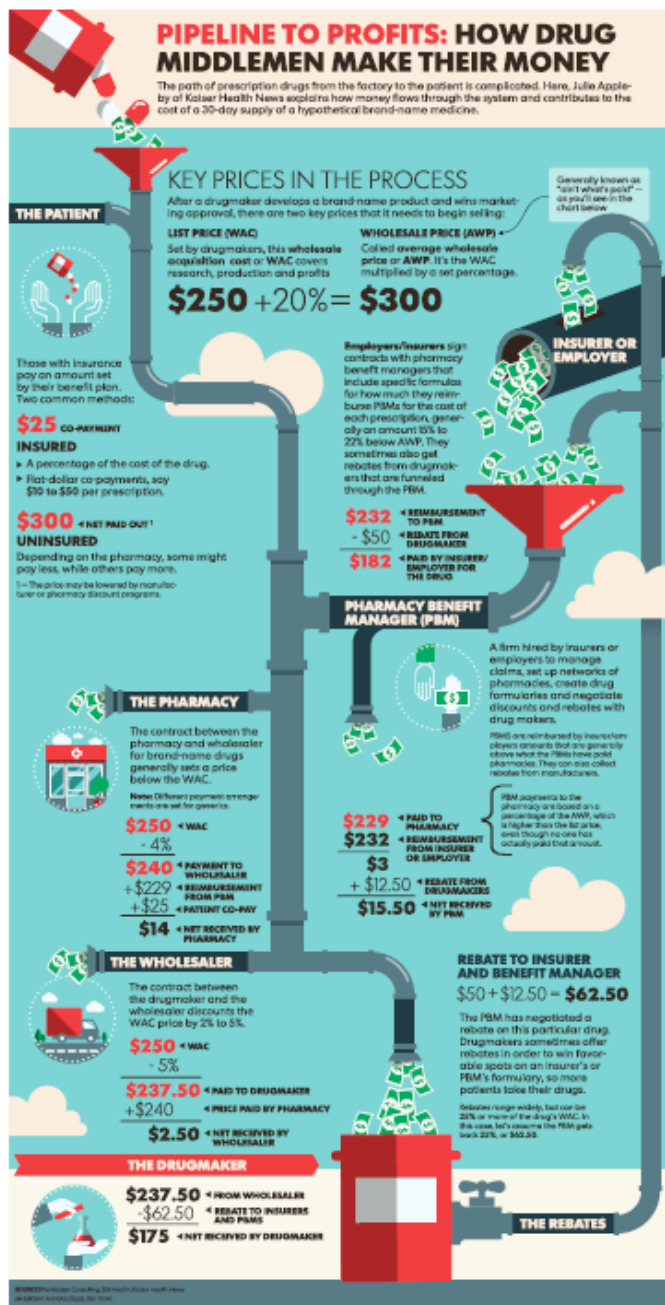


Figure 1. Pipeline to Profits: How Drug Middlemen Make Their Money

(USA Today, October 2, 2016)

Publicly Available Performance-Based Risk-Sharing Agreement (Carlson et al., 2010)			
Product(s)	Manufacturer	Payer	Scheme
Simvastatin	Merck	Patients and Insurers	Merck promised to refund patients and insurers up to 6 months of their prescription costs if simvastatin plus diet did not help them lower LDL cholesterol to target concentrations identified by their doctors.
Statins	Park Davis (Pfizer)	North Staffordshire Health Authority	Park Davis (Pfizer) agreed to rebate the North Staffordshire health authority if a defined patient population did not achieve a low density lipoprotein cholesterol concentration target of <3 mmol/l after using statins.
Interferon beta's or glatiramer acetate	Biogen, Schering, Teva/Aventis, Serono	NHS	Patients using interferon betas or glatiramer acetate are followed for 10 years with treatment effects determined every 2 years. Drug price reduced to maintain cost-effectiveness (£36,000/QALY).
Bosentan	Actelion Pharmaceuticals	Medicare Australia	Actelion pharmaceuticals agreed to link the price of bosentan for pulmonary arterial hypertension to the survival of patients followed in an observational study.
Bortezomib	Johnson and Johnson	NHS	J&J agreed to reimburse the NHS in either cash or product for patients who do not respond (response measure: 50% decrease in serum M protein) after four cycles of treatment with Velcade. Responding patients receive additional four cycles.
OncotypeDx	Genomic Health	United Healthcare	United Healthcare agreed to reimburse the OncotypeDx test for 18 months while it and Genomic Health monitor the results. If the number of women receiving chemotherapy exceeds an agreed upon threshold, even if the test suggests they do not need it, the insurer will negotiate a lower price.
Zoledronic acid	Novartis	Deutsche Angestellten-Krankenkasse (DAK)	Novartis will cover the drug costs of any patient who experiences a fracture within 1 year of being treated with zoledronic acid. In return, the insurer agrees to shift the treatment of its patients to zoledronic acid and ensure Novartis a share of the osteoporosis market.
Omalizumab	Novartis	NHS	Novartis offers UK hospitals replacement product for appropriately diagnosed, high-need omalizumab patients who fail to achieve target clinical response.
Sandimmun oral, myfortic or certican	Novartis	Deutsche Angestellten-Krankenkasse (DAK)	Novartis agrees to refund the cost of cyclosporin, mycophenol acid or everolimus if a patient loses his/her donor kidney.
Cetuximab	Merck	Primary Care Trust	Rebate direct to primary care trust for vials of cetuximab used for patients who do not achieve a pre-agreed clinical outcome ('nonresponders') at up to 6 weeks (up to an agreed maximum of 3200 mg).
Bortezomib and Johnson	Johnson and Johnson	Scottish Medicines Consortium	J&J agreed to reimburse the NHS in either cash or product for patients who do not respond (response measure: 50% decrease in serum M protein) after four cycles of treatment with Velcade. Responding patients receive additional four cycles.
Sitagliptin, sitagliptin + metformin	Merck	Cigna	Merck has agreed to link the amount that Cigna pays for the diabetes drugs sitagliptin, sitagliptin + metformin to how well type 2 diabetes patients are able to control their blood sugar.
Risedronate sodium	Proctor & Gamble, Sanofi-Aventis	Health Alliance	Two companies that jointly sell the osteoporosis drug risedronate sodium agreed to reimburse Health Alliance for the costs of treating-related fractures.
Nilotinib	Novartis	AIFA	Novartis has agreed to refund the cost of treatment with nilotinib for CML for every patient who does not reach an agreed hematological response after 1 month.

Table 2. Select Publicly Available Performance-Based Risk-Sharing Agreements (Carlson et al., 2010)

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