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ABSTRACT

Economic literature has extensively studied how prices for incumbent pharmaceutical drugs respond to generic competition after entry. However, less attention has been paid to pricing behavior in anticipation of brand-to-brand competition. We contribute to this gap in the literature by both developing a model of pricing strategies for incumbent drug manufacturers under tiered-insurance anticipating branded competition. Our model predicts rising prices for incumbent drugs for a range of elasticities as the likelihood of entry increases from competitors with horizontally-differentiated products. Using the insulin market as a natural experiment, we exploit exogenous variation in a potential entrant's completion of clinical trials to identify the effect of drug pipeline pressure on the prices of incumbent drugs. Results suggest that pipeline pressure significantly increases the prices of incumbent drugs. We expect that similar pricing effects will be prevalent with potential biosimilar entry.

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Several studies have recently documented rising prices for pharmaceuticals in various therapeutic areas, especially among branded drugs [Hua et al. (2016); Bennette et al. (2016); Hartung et al. (2015); Howard et al. (2015)]. Brand-name drugs account for 72 percent of drug spending, though they comprise only 10 percent of prescriptions dispensed in the U.S. [Kesselheim, Avorn and Sarpatwari (2016); Generic Pharmaceutical Association (2015); Express Scripts (2015)]. Among the most commonly used branded drugs, prices increased by about 164 percent between 2008 and 2015, greatly outpacing inflation (Office of the Assistant Secretary for Planning and Evaluation 2016). These trends are quite different from pricing trends observed in markets with generic drugs or over-the-counter drugs. Despite these considerable observed differences, the majority of our understanding in prescription drug pricing and entry relies on literature focused primarily on the competitive effects of generic drugs. The original prescription drug paradox referred to a phenomenon following generic entry whereby price-sensitive consumers switched to the generic and prices among brand name drugs subsequently rose as the remaining demand for brand name drugs was less elastic.

The ***new*** prescription drug paradox refers to a phenomenon of increasing prices corresponding with an increasing number of branded competitors. These escalating prices are perplexing given that as more treatment options become available over time, patients and insurers should have more flexibility and bargaining power in both drug choice and drug costs. Furthermore, these rising prices may be symptomatic of concerns highlighted by Dasgupta and Stiglitz (1988) that potential competition, and even competition itself, may not be sufficient to eliminate substantial market power in modern industries, especially those like healthcare and drug manufacturing where considerable Research & Development (R&D) is required and prices are not fully observable. In the current healthcare debate, understanding the role of competition and what it may and may not be able to accomplish is fundamental, especially in brand name competition. Therefore, there is a critical policy need to understand the role of brand name competition and potential competition to better inform policies addressing prescription drug prices.

We contribute to this policy debate by studying the effect of potential competition on pricing decisions of drug manufacturers under patent. Our analysis approaches this issue in two ways. First, we derive a model of branded pharmaceutical price competition under tiered insurance for incumbent drugs facing uncertain entry in the future. The intuition behind the model proposes that pharmaceutical firms have a long-term revenue maximizing strategy, where uncertain entry introduces a tradeoff between current revenue and future revenue. Branded drugs in the pipeline represent a kind of market exclusivity loss. Though an incumbent will be the only producer of a certain drug, other drugs which can serve as a therapeutic substitute can eat into the incumbent's market share. It may be revenue maximizing, and therefore profit maximizing, for the

incumbent to raise prices now and offset some of the revenue loss due to market share loss if/when entry occurs. This theoretical result relies largely on the incumbent manufacturer facing less elastic demand due to insurance. The tiered structure of prescription drug coverage incentivizing the entrant to reference price the incumbent's current market prices and horizontal differentiation between drugs. The model predicts that as the credible threat of entry increases, an incumbent drug manufacturer will increase price. It also allows for an entrant with a vertically-differentiated product to price higher than existing drugs, and demonstrates that following entry, price for the incumbent will decrease, but maintain a markup.

Second, we empirically test whether existing competitors adjust price in the presence of pipeline pressure, focusing on a particular drug market without entry but with an increasing amount of potential entry - insulin. This market provides a suitable natural experiment because there is no change in the composition of incumbent's over a span of several years, yet several potential entrants have new insulins in the drug development pipeline. We use clinical trial results to exploit exogenous variation in a potential entrant's success in different phases of the pipeline, and consider the change in price in quarters following pipeline shocks compared to quarters without pipeline shocks. Though the choice to start research & development (R&D) in a particular market will be endogenous with price, neither the timing of clinical trials clearance nor regulatory approval can be controlled by market participants. Therefore, the effect of competitive pressure on prices of incumbent manufacturers can be identified using pipeline shocks. Results indicate that pipeline shocks have significant effects on the price of incumbent insulins. Pipeline pressure significantly increases the prices of incumbent drugs, and potential biosimilar entry may drive this effect. Furthermore, pipeline shocks have cumulative effects. As the probability of entry of at least one or more new branded drugs increases, the pipeline shock effect becomes stronger. Both the third and fourth pipeline shocks increase prices among incumbent drugs by about $2.30 per shock. For the average patient taking about 12.48mL of insulin per month, this corresponds to about 30 additional dollars. However, the quality of information about the shock and the particular drug shock matters. In the insulin market, rising prices due to pipeline pressure are largely driven by a branded biosimiliar in the pipeline. These results are robust to several specification checks.

1 Background and Literature Review

1.1 The Drug Approval Process

Drugs available for treatment undergo a rigorous process before they are prescribed to patients. The drug approval process begins with pre-clinical research within a manufacturing firm. If a treatment provides

promising results from pre-clinical research, manufacturers submit an Investigational New Drug (IND) application, which is reviewed by the FDA's Center for Drug Evaluation and Research (CDER). If an IND application is approved, manufacturers begin clinical trials with people. These clinical trials are broken into three phases − Phase 1, Phase 2, and Phase 3 − where each subsequent phase indicates success in the previous phase. If all three phases of clinical trials are successful, then a manufacturer submits a New Drug Application (NDA) or Biologic License Application (BLA). The FDA reviews these applications and if a drug successfully demonstrates safety and efficacy, the drug will be approved for use in the United States.[1]

Drug patents and/or exclusivity awards are critical in this market. Patents are granted by the United States Patent and Trademark Office at any time, regardless of approval status, and carry a term of 20 years. Exclusivity awards place a delay and prohibitions on the approval of competitor drugs. Exclusivity takes effect once a drug receives FDA approval, with the longest possible exclusivity award, 7 years, applying to orphan drugs. According to the FDA, "patents and exclusivity may or may not run concurrently and may or may not cover the same aspects of the drug product."[2] Yet, both of these institutional awards grant a drug manufacturer monopoly power, which provides the incentives for pharmaceutical companies to invest in R&D for innovative treatments. Recent estimates of R&D costs per drug approval amount to about $2.87 billion (DiMasi, Grabowski and Hansen 2016), so these awards are critical to incentivize these incredibly risky investments. Most work studying the effect of entry on pharmaceutical prices focuses on generic entry. Generic drugs are pharmacologically-identical to their brand-name counterpart drugs. They have the same intended use, effects, side-effects, administration route, risks, safety, and dosage as the original drug. Drugs manufacturers are protected from generic competition during patent/exclusivity periods. When the period granted ends, a pharmaceutical product may face generic entry. However, drugs under the patent and/or exclusivity period may face competition from other patented drugs which obtain the same or similar therapeutic goal, but are not pharmacologically-identical to existing drugs, and therefore do not violate patent and/or exclusivity rules.

We will refer to this type of competition as brand-to-brand, brand-name, or branded competition. Note that in branded competition, it is possible to have both horizontally-differentiated and vertically-differentiated products. Horizontally-differentiated drugs are different, but the choice of which drug depends on the consumers preferences. Vertically-differentiated drugs are of different quality. Inn other words, drugs are different and all consumers would prefer one drug over the other. The patent process does not require

[1] More information on this process can be reviewed at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm

[2] More information on drug patents and exclusivity can be found at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm

that new drugs be vertically-differentiated. Manufacturers seeking FDA approval are only required to show that the drug's benefits outweigh its known risks and that the drug can be manufactured in a way that ensures its quality. Drugs are not required to show that they perform "better" than existing drugs on the market. Patents are awarded as long as the new drug has a formulation that is different from existing drugs. Therefore, it is possible to observe both vertical differentiation and/or horizontal differentiation in branded competition. "Me-too drugs" may be considered horizontally-differentiated drugs.

The amount of brand-to-brand competition an incumbent may face is considerably more uncertain than the threat of generic entry. Studies report that the clinical success rate − the product of individual phase transition probabilities for the clinical trials portion of drug development − is quite low, around one in ten (Hay et al. 2014). However, estimates from various studies indicate that success in phase 3 ranges from 55 to 64 percent [Abrantes-Metz, Adams and Metz (2004); Kola and Landis (2004); DiMasi et al. (2010); Hay et al. (2014)]. Thus, the credibility of the threat of entry increases considerably once a drug reaches phase 3. These studies also suggest that phase 3 success further increases the threat of entry. Estimates from the same set of studies indicate that between 77 - 93 percent that successfully complete phase 3 studies move on to NDA submission and approval.

1.2 Drug Price Competition

The economic field of industrial organization has extensively studied the game theoretic behavior of firms and how incumbent firms anticipate and respond to entry (Tirole 1988). Theoretical work largely demonstrates that under many circumstances entry − and even potential entry (Baumol, Panzar and Willig 1982) − can drive markets to the efficient allocation of resources. In many ways, competition has generally been regarded as a force which exerts "downward pressure on costs, reduces slack, provides incentives for the efficient organization of production, and even drives innovation forward" (Nickell 1996). It has also been largely regarded as a force to reduce price. Yet, theoretical work also suggests that there are a wide array of anticompetitive strategies a firm can employ to deter entry (Salop 1979). This prompted a series of econometric studies investigating the market effects of entry in various industries [Bresnahan and Reiss (1991); Berry (1992); Bunch and Smiley (1992); Mazzeo (2002); Pakes, Ostrovsky and Berry (2007); Aghion et al. (2009)]. The empirical work indicates that the incumbent response to entry is both mixed and selective (Geroski 1995).

This econometric work has important implications for the prescription drug pricing debate. It is not clear that competition, potential or actual, can be the silver bullet to the drug pricing dilemma. Research

following the passage of the 1984 Drug Price Competition and Patent Term Restoration Act indicated that generic competition was a driving effect in declining prices [Grabowski and Vernon (1992); Frank and Salkever (1997); Morton (1999); and Reiffen and Ward (2005)], with a minor caveat that market size and concentration may limit the speed and extent of the transition to lower priced generics (Tenn and Wendling 2014). Yet, this research also suggests that competition is not the only market incentive at play. Grabowski and Vernon (1992), Frank and Salkever (1997), and Ching (2010) all contend that there is considerable consumer heterogeneity in price-sensitivity which can produce differential effects on drug prices following entry. Ching (2010) also suggests consumers learning plays a role and incumbent manufacturers have an incentive to slowly raise prices, retaining as much market share as possible and slowing the learning process about new drugs.

Furthermore, research has indicated a variety of factors influence the price of prescription drugs, mostly factors that may mitigate the pressure from competition. Drug-level factors like innovation, the development of drugs with therapeutic gains from greater efficacy and/or safety relative to existing drugs [Reekie (1978) and Lu and Comanor (1998)], differentiation, both vertical and horizontal, and advertising increase drug prices [Perloff, Suslow and Seguin (1995); Bhattacharya and Vogt (2003); Ching (2010)]. Institutional-level factors like regulatory standards, patent protection, and market structure can also influence market efficiency and price dynamics [Danzon and Chao (2000); Kyle (2007); Brekke, Canta and Staume (2016)]. Additionally, the role of insurance as an institutional factor in drug pricing has largely been assumed away, despite a key detail that nearly all prescription drugs are provided through health insurance plans. Nearly all Americans obtaining health coverage through an employer have access to a plan with prescription drug coverage, and in most cases the worker has coverage without first meeting a deductible (Claxton et al. 2016). In addition, over 89% of these plans have tiered prescription drug coverage (Claxton et al. 2016). It is clear that prescription drug insurance will tie into consumer price-sensitivity [Lakdawalla and Sood (2009) and Berndt, McGuire and Newhouse (2011)].

We suspect that typical prescription drug insurance plans largely eliminate patient price-sensitivity resulting in a lack of downward pressure on price. Specifically, we conjecture that under this institutional structure, both incumbent drug manufacturers and potential entrants face a pricing decision under which increasing price is the dominant strategy. We contribute to the existing literature on anticipating entry and pharmaceutical competition in the following ways. First, we explore the effect of pressure in the pipeline on prescription drugs. The aforementioned econometric work has focused on the effects of actual entry, because it is not often possible to observe *potential* entry. However, in the case of pharmaceuticals, information from

the drug development pipeline is publicly available due to the Food and Drug Administration Modernization Act (FDAMA) of 1997 requiring trial registry. Therefore, we can directly observe potential competitors in the pipeline and identify the effect of the credible threat of entry on incumbent pricing strategies. Second, we develop a two-period model of pricing strategies under tiered prescription drug insurance for an incumbent drug manufacturer. The model predicts rising prices for incumbent drugs for a range of elasticities as the likelihood of entry increases. Third, we econometrically assess pricing adjustments due to pipeline pressure, using the insulin market as a natural experiment. Finally and perhaps most importantly, we contribute to the growing assessments of pharmaceutical competition. Policy-makers may expect entry and competition to improve consumer welfare, but we find evidence that this wishful thinking is unlikely to be true.

1.3 A Motivating Example: Insulin

Insulin is a life-saving drug used to treat diabetes.[3] It helps patients maintain glycemic control and prevent and/or delay considerable complications and costs. On average, medical expenditures in the US are approximately 2.3 times higher for patients with diabetes than those without, and it accounts for more than 1 in 5 health care dollars spent (Yang et al. 2013). Therefore, consistent treatment with insulin can be both beneficial to patients and the US healthcare system. This particular drug is a biologic, originally discovered and patented in the early 1920s, marking a monumental improvement in treating patients with diabetes. In the last 95 years, incremental improvements in safety, efficacy, and convenience have characterized the market for insulin. Older versions of insulin were derived from animal and human DNA. The newest version of insulin which is derived from recombinant DNA (rDNA), the insulin analogue, was introduced on the U.S. market in 1996. Animal and human insulins are considered somewhat inferior in both efficacy and safety to insulin analogues,[4] and used less frequently.

Recent research reports that the price of insulin has soared in the previous decade. Hua et al. (2016) report that the price of insulin, measured as the mean price per milliliter, rose 197 percent from 2002 to 2013. Between 2007 and 2014, there were no new insulin analogues approved by regulatory agencies, but there were several in pipeline development. Various insulins in drug development completed the final phase of clinical trials and submitted national drug applications (NDAs) in the following quarters: 2009q1, 2011q3, 2013q4, 2014q2. Despite the rising threat of potential competition, Figure 1 depicts that the average inflation-adjusted price of insulin per mL is increasing over time, from $14.67 at the beginning of 2007 to

[3]It is the only treatment for type 1 diabetes, and is used as a second and/or third line therapy for type 2 diabetes when other treatments are unsuccessful.

[4]Insulin analogues both improved glycemic control and reduced the rate of adverse events in the form of severe hypoglycemia, two life-threatening issues for patients with this condition, compared to earlier versions of insulin like animal and human.

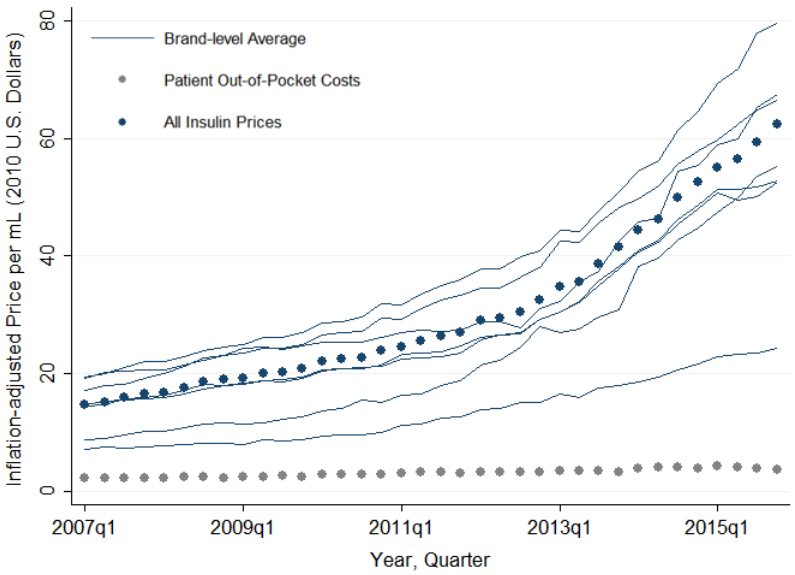

Figure 1: Average Prices for all Insulin Prescriptions, 2007-2015

$61.22 by the end of 2015. On average, this is a 317.3 percent increase in the price of incumbent insulins. The majority of these price increases were absorbed by payers, though this could be dampened by the size of rebates. Payments made by patients increased by 56 percent.

2 Brand Name Drug Competition with Uncertain Entry

Consider a drug manufacturer in a two-period model facing uncertain entry in the second period. In the first period, the drug manufacturer is a monopolist. This drug is a brand name drug under patent. Entry in the second period is probabilistic. Therefore, the monopolist is referred to as the "incumbent" and a new "entrant" firm may enter the market. If entry occurs, the entrant firm produces a branded drug which is qualitatively similar to the incumbent's product but considered to be an imperfect substitute. This is because, the entrant's drug may have limited information on effectiveness at regulatory approval, while patients requiring treatment for this drug have experience with the incumbent's drug for consumers. Therefore, the differentiation between the incumbent's and the entrant's drug is horizontal and driven by patient preferences, doctor preferences, or some other implicit preference to try the new treatment. After observing price in the first period, there is some probability that entry occurs and both the incumbent and entrant simultaneously set a price in the second period.

In the presence of insurance, the demand price faced by the consumer is vastly different from the market

price that a monopoly may set. In fact, in many cases an insurer would only charge a fixed copay from the beneficiaries for a drug. The insurer pays the rest of the price. Berndt, McGuire and Newhouse (2011) demonstrate that coinsurance makes demand less elastic and suggest that plans with fixed copayments will result in even higher prices with price increases translated into higher premiums. Consequently, consumer demand for this drug is inelastic, giving the monopolist an opportunity to set a price that can extract rents from the market. This is unlike a traditional monopolist whose price is constrained directly by the elasticity of consumers. The final price set by the monopolist would involve negotiations with the insurer so that the price would preserve a non-negative profit margin for the insurer. For our purposes, we do not need to explicitly consider the specific form of insurer constraint. Whatever it is, we acknowledge that it is used to set equilibrium prices. Furthermore, we acknowledge that the presence of uncertainty, imperfect information, and insurance can have a significant effect on markets as demonstrated by Rothschild and Stiglitz (1976) and Arrow (1963). Without modeling these details, this model attempts to outline the incentives for a drug manufacturer whose demand is largely supplied by insurance. Our goal is to see if the equilibrium price prior to entry is influenced by other factors, especially pressure from the drug development pipeline, or potential competition.

2.1 Extensive Form of the Two Period Model

There are two participants, the incumbent and the entrant. In the first period, the incumbent chooses price. In the second period, both the entrant and the incumbent make a simultaneous choice on price. The incumbent has complete but imperfect information about the likelihood of entry in the second period. Let subscript i represent the incumbent firm and subscript e denote the entrant firm. In addition, let subscript $1, 2$ denote the period of the game. Then, for example, term R_i is the incumbent's revenue, and P_{1i}, c_{1i}, and Q_{1i} denote the incumbent's price, copayment, and quantity in the first period, respectively. There are three formal assumptions that are required.

Assumption 1. *Each product in the market is available to consumers at a constant demand price (for example, a set copay) via insurance.*

Assumption 2. *Without loss of generality, marginal costs are zero for each drug.*

Assumption 3. *Drugs are homogenous in terms of clinical benefit. That is, they are therapeutically equivalent in treatment, but may exhibit other quality attributes that are more or less desirable according to patient preferences.*

Assumption 4. *Under tiered prescription drug insurance, a lower price generates a more favorable tier placement, and therefore a lower copay charged. That is, if the entrant sets a price* $P_e = \gamma P_i$ *where* $\gamma \leq 1$*, and the copayment is a function of the fraction of price charged,* $c_e = c_e(\gamma)$*, copayments can be anchored at* $c_e(0) = 0$ *and* $c_e(1) = c_i$ *where setting price equivalent to the incumbent dictates that the two drugs be placed on the same insurance tier. It follows that the elasticity of copayment with respect to price is linear,* $\frac{\partial ci}{\partial P_i} = \frac{c_i}{P_i}$ *and* $\frac{\partial c_e}{\partial P_e} = \frac{c_e}{P_e}$ *in both periods.*

In what follows, we solve for a Sub-game Perfect Nash Equilibrium (SPNE) using backward induction (Selton 1965) and the aforementioned Assumptions. Therefore, we will first find best response functions, the optimal strategy for a particular player given the strategies of other players, for both players in the second period, and use these expectations to examine the pricing strategy for the incumbent in the first period.

2.2 Equilibrium Strategy for the Entrant

First, consider the equilibrium strategy for the entrant. Let price set by the entrant be $P_{2e} = \gamma P_{2i}$ where $\gamma \leq 1$ and denotes the fraction the entrant sets its price in reference to P_{2i}. Let $c_{2e} = c_{2e}(\gamma)$ where c_{2e} denotes the copayment that the insurer charges for the entrant's drug in the second period. Naturally, $c_{2e}(\gamma) \leq c_{2i} \forall \gamma$ and $c'_{2e} = \frac{\partial c_{2e}}{\partial \gamma} > 0$, that is, a lower price of the entrant's product would lead to the lower copay charged. Let $c_{2e}(\gamma)$ be linear in γ. Since $c_{2e}(0) = 0$ and $c_{2e}(1) = c_{2i}$, then $c'_{2e} = c_{2i}$. It follows that for both the incumbent and the entrant, the elasticity of copayment with respect to price is 1, that is, $\frac{\partial ci}{\partial P_i} = \frac{c_i}{P_i}$ and $\frac{\partial c_e}{\partial P_e} = \frac{c_e}{P_e}$ in both periods. In the second period, if a new manufacturer gets regulatory approval to enter the market with a qualitatively similar but imperfect substitute to the incumbent's drug, the pricing decision follows a simultaneous game where the incumbent and the entrant are trying to price their own products anticipating competition from the other, albeit in the presence of insurance. Like the incumbent, the entrant is also subject to the demand price separation due to insurance that protects it from the full price-elasticity of consumer demand. Let the demand function for the entrant be given as

$$Q_{2e} = a - b_1 c_{2e} + b_2 c_{2i} \tag{1}$$

where c_{2e} and c_{2i} are the copayments set for the entrant's and incumbent's drugs, respectively, by the insurer. Here b_1 captures the responsiveness of the entrant's demand with respect to its own copayment, while b_2 captures the responsiveness with respect to the incumbent's copayment. a denotes the demand intercept facing the entrant.

If the insurer covers both drugs at the same copayment level (i.e. $c_{2e} = c_{2i}$), and there are no restrictions set on which drug the patient chooses to take, switching to the entrant's drug is determined entirely by patient preferences, doctor preferences, or some other implicit preference to try the new treatment. Both the incumbent and entrant drug can achieve the same treatment goal, but rather switching to the new drug is determined by underlying preferences. Gaynor, Propper and Seiler (2016) and Santos, Gravelle and Propper (2017) demonstrate that certain quality characteristics matter in this type of discrete choice between products and/or providers in healthcare, specifically considering patient choice among hospitals in the English National Health Service. As previously mentioned, we assume that products in this theoretical model are horizontally differentiated, so that switching to the new drug is not driven by vertical differences in quality. Let there be some portion, θ, of the population demanding treatment for this condition, Q, at a copay of c_{2i} who will switch to the entrant's drug under these conditions, leaving a fraction $(1 - \theta)$ for the incumbent's demand. Therefore, following a linear inverse demand function for the entrant's drug under this condition is

$$Q_{2e} = \theta Q = a - b_1 c_{2i} + b_2 c_{2i} \implies a = \theta Q + c_{2i}(b_1 - b_2) \tag{2}$$

Under such a scenario, there is no reason for the entrant to price its drug any differently than the current prevalent price of the monopolist, i.e. $P_{2e} = P_{2i}$. This is because P_{2i} is the maximum price the entrant can charge in this simultaneous game, which maximizes its revenues since θQ is outside of entrant control.

However, since insurers often utilize a tiered system of copays to induce price elasticity of demand between two products, the entrant will have a pricing decision at hand. Specifically, the entrant debates whether to charge a lower price than P_{1i} so that its product may be placed in a higher tier, (i.e. lower copayment) than the monopolist incumbent's product. Would the demand surge due to this favorable placement be enough to overcome the shortfall in revenue due to the lower price? To answer this question, we solve the entrant's revenue maximization problem as follows. The entrant will maximize revenue in the second period, which also maximizes profit. This is given by

$$\max_{P_{2e}} R_e = P_{2e} \cdot Q_{2e} \tag{3}$$

Substituting for Q_{2e} using Equation 2, we can rewrite the entrant's second-period problem as

$$\max R_e = P_{2e} \cdot Q_{2e} = P_{2e}\big[a - b_1 c_{2e} + b_2 c_{2i}\big]$$

Solving the entrant's first-order condition with respect to P_{2e}, setting this equal to zero, and solving for

P_{2e} generates the best response function for the entrant. The best response function describes the optimal strategy for a particular player, here the entrant, given the strategies of other players, here the incumbent. To simplify the entrant's best response function, we apply Assumption 4 and Equation 2 as well as requiring that $\frac{c_{2e}}{P_{2e}} = \frac{c_{1i}}{P_{1i}}$ and $\frac{c_{2i}}{P_{2i}} = \frac{c_{1i}}{P_{1i}}$.

$$P_{2e} = \frac{\theta Q P_{1i}}{2b_1 c_{1i}} + \frac{1}{2} P_{2i} \tag{4}$$

Equation 4 displays the entrant's best response function. Note that if $\theta = 0$, that is, no one switches to the entrant's drug, the entrant prices the new drug at half the incumbent's price. Notice also that this suggests the entrant may increase price over the incumbent's drug, if the market share gain is high relative to the elasticity with respect to copay. In fact, if the entrant's product is substantially differentiated vertically, and therefore the entrant captures a larger share of demand, the entrant may price considerably higher than the incumbent price.

2.3 Equilibrium Strategy for the Incumbent

The incumbent two-period decision problem is given as

$$\max_{P_{1i}, P_{2i}} R_i = P_{1i} \cdot Q_{1i} + E(R_{2i}) \tag{5}$$

where P, Q, and R denote price, quantity, and revenue, respectively. In drug manufacturing, fixed costs are high and sunk, and marginal costs of production are low. Therefore, by Assumption 2, maximizing revenue is equivalent to maximizing profit. Note that although the monopolist can set prices with certainty in the first period and thereby determine revenue, it faces uncertainty about the second period stream of revenue due to the potential entry of the entrant's product. Let the probability of an entrant entering the market in period 2 be denote by ρ. Hence the incumbent's problem can be written as:

$$\max R_i = P_{1i} \cdot Q_{1i} + \left[(1-\rho) P_{1i} \cdot Q_{1i} + \rho P_{2i} \cdot Q_{2i}\right] \tag{6}$$

We can also find a best response function for the incumbent in the second period based on the entrant's best response. Like the entrant, the incumbent also faces demand separation. Let the inverse demand function for the incumbent in the second period be given as

$$Q_{2i} = \alpha - \beta_1 c_{2i} + \beta_2 c_{2e} \tag{7}$$

From the demand function of the entrant, we know that if the copayments for both products are the same, there is a shift of demand of θQ from the incumbent to the entrant for reasons other than demand prices. By construction, this also means that there is no brand loyalty strategy that can alter the size of θ. Therefore, at equal copay, (7) can be written as:

$$Q_{2i} = (1-\theta)Q = \alpha - \beta_1 c_{2i} + \beta_2 c_{2e} \implies \alpha = (1-\theta)Q + c_{2i}(\beta_1 - \beta_2) \tag{8}$$

Next, we will find the incumbent's best response function in the second period, using the entrant's best response function. Since we are seeking an SPNE using backward induction, we must consider the incumbent's second period decision. The incumbent will maximize revenue in the second period given by

$$\max P_{2i} \cdot Q_{2i} = P_{2i} \cdot \left[\alpha - \beta_1 c_{2i} + \beta_2 c_{2e}\right] \tag{9}$$

By simplifying using the entrant's best response function from Equation 4 as well as $\frac{c_{2e}}{P_{2e}} = \frac{c_{1i}}{P_{1i}}$ and $\frac{c_{2i}}{P_{2i}} = \frac{c_{1i}}{P_{1i}}$, we can describe the incumbent's second period maximization problem only in terms of incumbent's prices. This is given by

$$\max P_{2i} \cdot Q_{2i} = P_{2i} \cdot \left[\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} \left(\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i}\right)\right] \tag{10}$$

Taking the incumbent's first-order condition with respect to P_{2i} and solving for P_{2i} in terms of P_{1i} gives

$$P_{2i} = P_{1i} \frac{\alpha + \beta_2 \frac{\theta Q}{2 b_1}}{c_{1i}(2\beta_1 - \beta_2)} \tag{11}$$

Equation 11 describes the incumbent's best response function.

Theorem 1. *Under Equations 4 and 11, the incumbent will raise its market price in period 1 if the probability of an entrant entering the market in period 2 increases, i.e.* $\frac{dP_{1i}}{d\rho} > 0$.

Recall the incumbent's problem in Equation (6),

$$\max R_i = P_{1i} \cdot Q_{1i} + \left[(1-\rho) P_{1i} \cdot Q_{1i} + \rho P_{2i} \cdot Q_{2i}\right] \tag{12}$$

Replacing Q_{2i} using Equation 7 and replacing Q_{1i} assuming that $Q_{1i} = Q$, i.e. the incumbent was meeting the full demand in period 1 at the copay of c_{2i}. Furthermore, the inverse demand function for the incumbent in the first period is $Q_{1i} = \alpha - \beta_1 \cdot c_{1i}$, where the elasticity of copayment with respect to price is 1 (following

Assumption 4), i.e. $\frac{\partial c_{1i}}{\partial P_{1i}} = \frac{c_{1i}}{P_{1i}}$. To simplify expressions, let $\omega = \frac{\alpha+\beta_2\frac{\theta Q}{2b_1}}{2\beta_1-\beta_2} \implies P_{2i} = \omega\frac{P_{1i}}{c_{1i}}$. After simplification presented fully in the Appendix, we can rewrite the incumbent's problem in (12) as

$$\max_{P_{1i}} R_i = P_{1i}\cdot(\alpha-\beta_1\cdot c_{1i}) + (1-\rho)P_{1i}\cdot(\alpha-\beta_1\cdot c_{1i}) + \rho\omega\frac{P_{1i}}{c_{1i}}\Big(\alpha-\beta_1\omega+\beta_2\Big[\frac{\theta Q}{2b_1}+\frac{1}{2}\omega\Big]\Big) \tag{13}$$

Next, we differentiate the incumbent's revenue with respect to price and set this equal to zero yields the incumbent's first-order condition with respect to P_{1i}. After simplifying this expression, we have

$$2\alpha - 4\beta_1 c_{1i} - \alpha\rho + \rho 2\beta_1 c_{1i} = 0 \tag{14}$$

This condition is based on both the entrant and the incumbent choosing optimal strategies according to the SPNE. We are not necessarily concerned with the equilibrium, but rather how equilibrium pricing in the first period changes as the probability of entry changes. In other words, when $\frac{dP_{1i}}{d\rho} \geq 0$, the incumbent will increase price in the first-period as the probability of entry increases. To assess this, we use implicit function differentiation. Therefore, the incumbent will raise first-period price as long as the following inequality is true.

$$\frac{\mathrm{d}P_{1i}}{\mathrm{d}\rho} = \frac{2\beta_1\frac{c_{1i}}{P_{1i}}(\rho-2)}{2\beta_1 c_{1i}-\alpha} \geq 0 \tag{15}$$

What conditions are required to observe this effect? Note that by definition $0 < \rho < 1$, and $2\beta_1\frac{c_{1i}}{P_{1i}} > 0$, so the numerator will be negative. Therefore, we must find conditions under which the denominator is also negative, or when $2\beta_1 c_{1i} - \alpha < 0$. Recall that demand facing the incumbent in the first period is $Q_{1i} = \alpha - \beta_1\cdot c_{1i}$. Elasticity for this demand curve is given by

$$\varepsilon = \frac{\partial Q}{\partial P}\cdot\frac{P}{Q} = -\beta_1\frac{c_{1i}}{P_{1i}}\cdot\frac{P_{1i}}{Q_{1i}} = -\beta_1\frac{c_{1i}}{Q_{1i}} \implies \varepsilon = \frac{-\beta_1 c_{1i}}{\alpha-\beta_1 c_{1i}} \implies |\varepsilon| = \frac{\beta_1 c_{1i}}{\alpha-\beta_1 c_{1i}}$$

For what elasticity will $2\beta_1 c_{1i} - \alpha < 0$ be true? Suppose elasticity for prescription drugs is 0.20 as indicated

in the RAND Health Insurance Experiment. Then,

$$\begin{aligned}
\varepsilon = \frac{\beta_1 c_{1i}}{\alpha - \beta_1 c_{1i}} &< 0.2 \\
\beta_1 c_{1i} &< 0.2(\alpha - \beta_1 c_{1i}) \\
\beta_1 c_{1i} + 0.2\beta_1 c_{1i} &< 0.2\alpha \\
\beta_1 c_{1i} - \frac{1}{6}\alpha &< 0 \\
2\beta_1 c_{1i} - \frac{1}{3}\alpha &< 0
\end{aligned}$$

As long as $\alpha > 1$, $2\beta_1 c_{1i} - \frac{1}{3}\alpha < 0 \implies 2\beta_1 c_{1i} - \alpha < 0$. Since α is a demand intercept, this is almost certainly the case. Therefore, the incumbent will increase price in the first period as the probability of entry is increasing. In fact, we can verify that this condition will be satisfied as long as $|\varepsilon| \leq 1$. Many prescription drugs face relatively inelastic demand, especially those that are life-saving. Therefore, this range of elasticity is likely to be satisfied, especially in the market we consider empirically. In what follows, we consider the price effects of pipeline pressure in a particular drug market, insulin.

3 Empirical Strategy: Pipeline Pressure in the Insulin Market

News of potential competition in the pipeline becomes available as entrants clear various phases of drug development and publish the results from clinical trials. As each phase of development is cleared, the likelihood of competing with at least one entrant increases, and incumbent firms may adjust their expectations about future competition. This news from the pipeline serves as an exogenous shock to the existing market. The completion of potential entrant clinical trials determine the timing of these shocks, not existing competitors. Therefore, news of potential entry will be regressed on the prices of existing insulin drugs. We model price as

$$P_{it} = \alpha_i + \theta_1 t + \theta_2 t^2 + \mathbf{Qtr}_{2,3,4}\boldsymbol{\eta} + \mathbf{X}_{it}\boldsymbol{\beta} + \mathbf{PipelineShocks}_{it}\boldsymbol{\delta} + u_{it} \tag{16}$$

where P_{it} is the price of drug i in quarter t, defined as average (median) payments for one mL supply. α_i are drug-level fixed effects which control for time-constant drug characteristics. This can include product differentiation, like higher concentration insulins, characteristics that affect ease of use, and therapeutic gains over existing drugs. t denotes time since the first phase 3 clearance of a potential competitor and captures continuous trends in price. $\mathbf{Qtr}_{2,3,4}$ is equal to one in the second, third, and fourth quarters, respectively, of

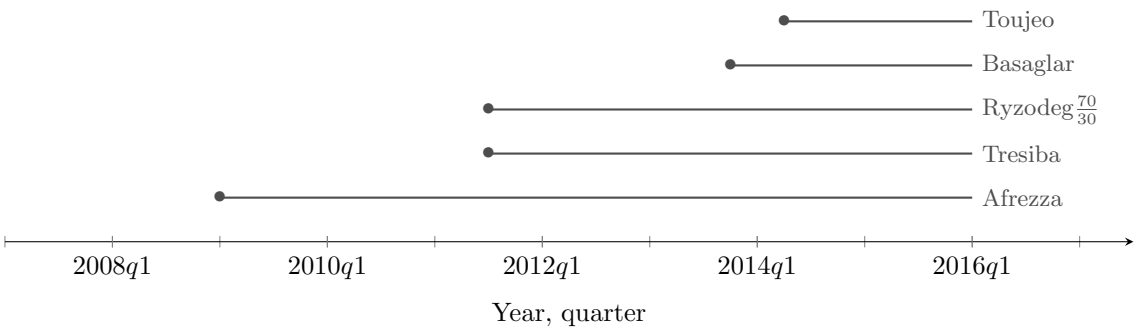

Figure 2: Pipeline Shocks, Completion of Phase 3 of Drug Development

the year which capture yearly cyclical trends in price. $\mathbf{X}_{it}$ includes market characteristics like the number of quarters the drug was on the market at baseline, and the health plan type providing coverage. Length of time on the market may also impact the pricing decision. More established brands may feel less pressure if they have had an ample amount of time to build brand loyalty to their product. Bhattacharya and Vogt (2003) establish this strategy, intended on increasing market share and improving brand loyalty to the drug, prior to generic entry. u_{it} is the idiosyncratic error, assumed to be independently and identically distributed.

Finally, $\mathbf{PipelineShocks}_{it}$ is the main factor of interest in this analysis and represents exogenous shocks from the drug development pipeline. In the initial specification, we consider the strongest signal of potential entry, completion of phase 3 clinical trials. We use the first national drug application (NDA) submission to mark successful completion of phase 3 trials.[5] $\mathbf{PipelineShocks}_{it}$ is a vector of a series of indicators which mark each additional completion of Phase 3 by a new potential entrant.[6] Table 8 in the Appendix lists all the clinical trials on record for insulins in the clinical trials phase of development during our panel. Figure 2 depicts how the $\mathbf{PipelineShocks}_{it}$ indicators are constructed for Phase 3 using information from Table 8. Once a drug in development clears a particular phase, a new indicator is created and the indicator stays on, i.e. is equal to one, for the remainder of the panel. Note that in some cases, information about more than one drug in the pipeline comes out at the same time. Therefore, this information will be represented jointly by one indicator, since separate effects cannot be estimated.

[5]Both Tresiba and Ryzodeg $\frac{70}{30}$ have an intial NDA submission, which is resubmitted in the first quarter of 2015. Existing drug manufacturers will likely internalize the information from the initial NDA submission in their price setting strategy, so the subsequent submission is not considered.

[6]In other specifications, we also consider the informational shocks from Phase 1 and Phase 2.

4 Data

Data on insulin prices was obtained from Truven Marketscan Commercial and Medicare Claims from 2007-2015. This resource includes individual-specific healthcare enrollment, utilization, and expenditure data from inpatient, outpatient, prescription drug, and carve-out services. MarketScan databases include both commercial claims, and medicaid and medicare supplements. All claims from Truven Marketscan from January 1, 2007 to December 31, 2015 with national drug codes (NDC) for all types of insulin were included in this analysis. These NDCs are listed in Table 9 in the Appendix. Claims were included for all enrollees regardless of age, insurance type, or diabetes type (diagnosis codes). We excluded claims where the enrollee identification number was missing (less than one percent of claims), and claims that were not fully adjudicated (less than 1.3 percent of claims).[7] In addition, claims for other anti-hyperglycemic medications were not included in this analysis.[8] After implementing these criterion on all insulin claims, there are 28,801,450 claims. The vast majority of claims (28,388,234 claims or 98.56 percent of claims) are for incumbent drugs, whose prices are considered in the analysis. In total, 87.2 percent of claims are for insulin analogues, the most modern form of insulin.

The price, the main outcome of interest, was calculated as total expenditures per patient for a one mililiter (mL) supply of each drug in each quarter adjusted for inflation using the urban consumer price index (CPI). Expenditures include payments from patients (copayments and coinsurance) and payments from the health plan. Health plan payments reflect a reduced payment after discounts are applied, but before rebates are transferred. Patient prices for a thirty-day, one mL supply were also computed. These patient prices include both copayments and coinsurance, depending on the construction of the health plan. In most cases, only a copayment or coinsurance is required. Figure 3 depicts the distribution of insulin price. Prices are considerably positively skewed with a long tail on the right hand side. However, over 95.9 percent of prices are concentrated between 0 and 100. Sensitivity checks were conducted to determine whether this significantly changes the results we obtain.

The following graphics derived from insulin claims are informative. Figure 4 depicts the frequency of claims for insulin by health plan type.[9] The majority of claims, 56.94 percent, are provided by PPO plans.

[7] When a claim does not match on all required criteria, adjustments cannot be made. This is a very small portion of the sample.

[8] These drugs are not typically used to treat patients with type 1 diabetes and among patients with type 2 diabetes they are used as a first-line treatment. Type 2 patients demanding insulin will likely have already tried these alternate therapies without success, or they may use these drugs in conjunction with insulin.

[9] There are nine health plan types: 1 − basic major medical, 2 − comprehensive (COMP), 3 − exclusive provider organization (EPO), 4 − health maintenance organization (HMO), 5 − non-capitated point of service (Non-cap POS), 6 − preferred provider organization (PPO), 7 − capitated or partially-capitated point-of-service (Cap or Part-Cap POS), 8 − consumer driven health plan (CDHP), and 9 − high deductible health plan (HDHP).

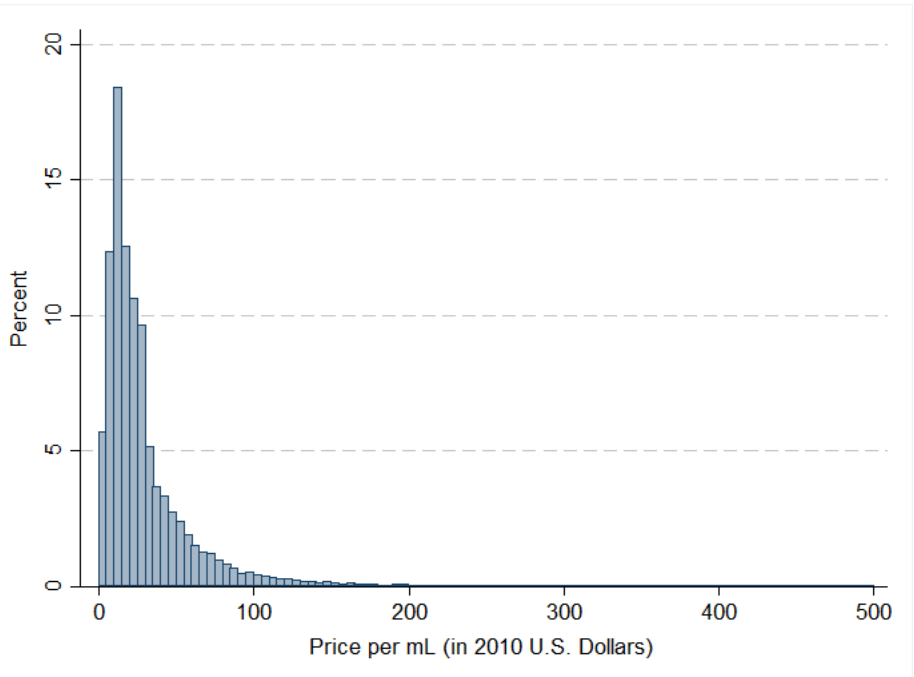

Figure 3: Distribution of Insulin Price

The next most common plan providers are HMO plans, 16.42 percent, and comprehensive plans, 12.36 percent. Figure 5 depicts the frequency of claims for insulin by brand. The most commonly used insulin brand is Lantus, 39.73 percent of all claims. Novolog and Humalog are the next most commonly used insulin brands, 20.30 and 17.85 percent, respectively.

The claims data was supplemented with additional data on drug characteristics obtained from Redbook and the Food and Drug Administration (FDA) Orangebook and Drugs@FDA database as well as information about drugs in the development pipeline from the United States Clinical Trials Online Registry. Drug attributes are matched to claims using the national drug code (NDC). Each national drug code identifies the size in mililiters (mL), a description of the packaging, the strength in units per mL (U/mL), the mechanism of action (peak, onset, and duration of the drug), and the insulin form (animal, human or analogue). We also obtain information on patents for each drug, and the patent expiration date to identify loss of exclusivity.[10] Finally, pipeline shock indicators described previously are constructed using information from the United States Clinical Trials Online Registry and from the Drugs@FDA database. This information is consolidated for this analysis and listed in Table 8 in the Appendix.

Table 1 presents summary statistics for variables used in the analysis which are partitioned by market

[10]Of all insulin products under patent, those with patent expirations prior to 2017 are discontinued. The earliest loss of exclusivity of drugs considered here is June 20, 2017.

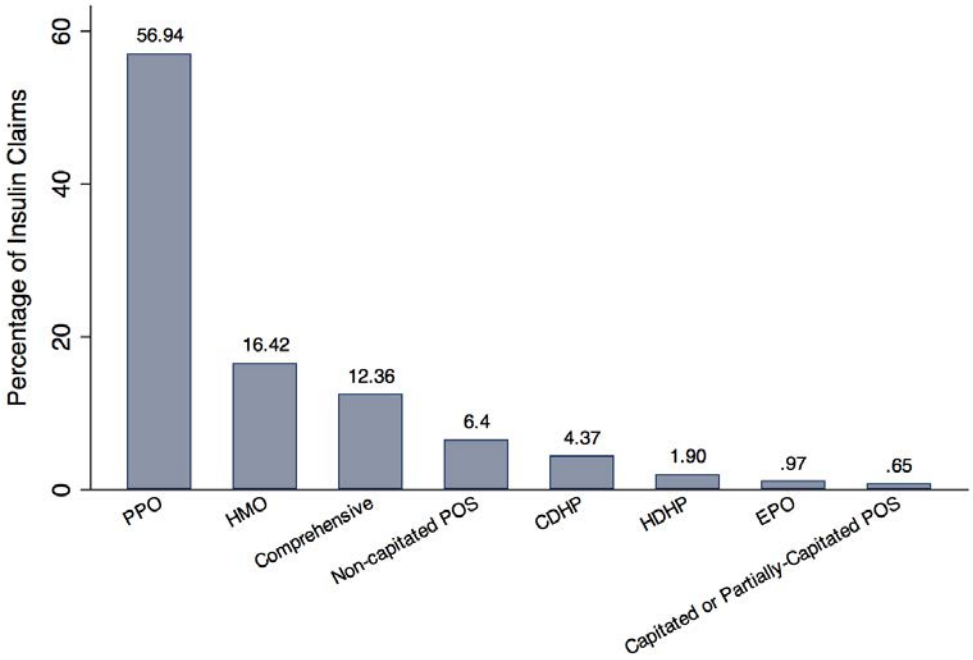

Figure 4: Percentage of Insulin Claims by Health Plan Type

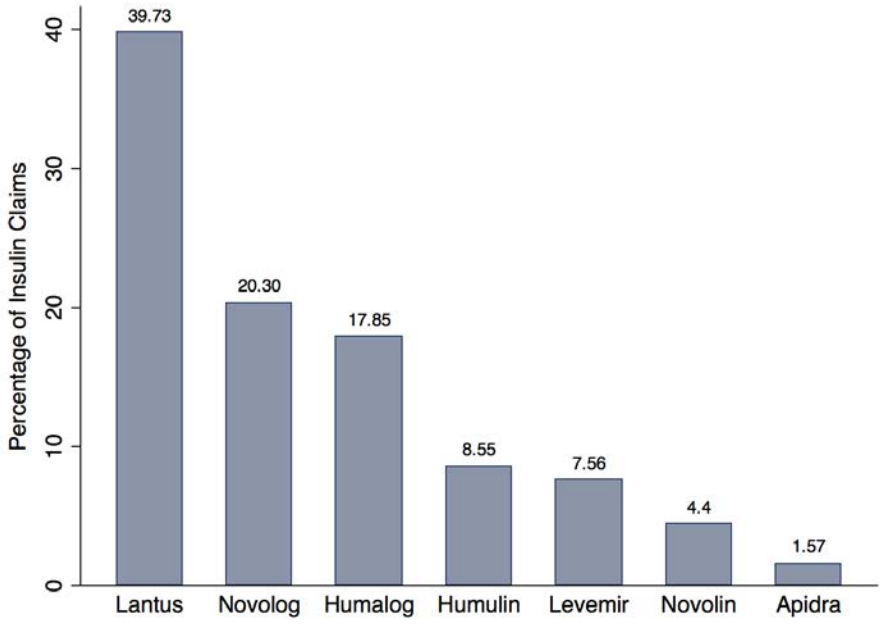

Figure 5: Percentage of Insulin Claims by Brand

Table 1: Summary Statistics

Incumbent Insulins, 2007q1 to 2015q4

Variable	Mean	Median	Std. Dev.	Min	Max
Price	30.46	20.42	33.63	0	3,074.73
Patient Price	3.04	2.34	3.62	0	784.93
Baseline Time on Market (in quarters)	35.50	27	22.61	4	100
Market Share, by NDC	0.12	0.09	0.09	0	0.32
Market Share, by Brand	0.25	0.20	0.13	0	0.41

Note. Summary statistics presented above, Incumbent Insulins, are calculated using observations included in the analysis.

Entrant Insulins, 2015q1 to 2015q4

Variable	Mean	Median	Std. Dev.	Min	Max
Price	138.25	83.58	134.71	0	3,251.93
Patient Price	13.73	9.73	24.30	0	1,220.07
Baseline Time on Market (in quarters)	-31.86	-32	0.73	-34	-29
Market Share, by NDC	0.02	0.03	0.01	0	0.03
Market Share, by Brand	0.02	0.03	0.01	0	0.03

Note. Summary statistics presented above, Entrant Insulins, are calculated using post-entry observations. They are for reference purposes only and are not included in the analysis which follows.

participation status. Incumbent drugs are insulins with approvals prior to the start of the panel. Entrant drugs are insulins in stages of the drug development pipeline during the panel. The analysis which follows considers only the prices of incumbent insulins, so the presentation of summary statistics for entrant insulins is only for informational purposes. There are several intuitive and revealing insights from this segmentation. First, median prices tend to be lower than average prices for both incumbent insulins and entrant insulins. The average time on the market for incumbent insulins at baseline (2007q1) is 35.5 quarters, over 8 years, and baseline time of the market for entrants is negative, by definition. Both prices and patient prices tend to be higher for entering drugs compared to incumbent drugs, indicating that new products may be vertically differentiated from existing products and therefore prices exhibit a markup. Market share tends to be higher for incumbent drugs compared to entrants, whether it is calculated by National Drug Code or by brand. In fact, the degree of market share loss immediately following entry in this market is quite low.

Table 2: The Effect of Phase 3 Pipeline News Shocks on Incumbent Insulin Prices

Variable	(1) Full Sample	(2) Analogue Only	(3) Human Only
Phase 3 Shocks			
1^{st} Pipeline Shock$_t$	-0.726	-0.678	-1.215
	(0.795)	(0.917)	(0.790)
2^{nd} Pipeline Shock$_t$	-1.147	-1.247	-0.312
	(0.912)	(1.076)	(1.116)
3^{rd} Pipeline Shock$_t$	2.285**	2.350**	0.654
	(1.053)	(1.103)	(2.054)
4^{th} Pipeline Shock$_t$	2.263**	2.284*	1.117
	(1.142)	(1.178)	(2.177)
Time	0.715***	0.810***	0.447***
	(0.0957)	(0.110)	(0.0838)
Time^2	0.0323***	0.0311***	0.0252***
	(0.00636)	(0.00709)	(0.00763)
Quarter 2	-0.643	-0.678	-0.443
	(0.455)	(0.517)	(0.534)
Quarter 3	-0.278	-0.312	-0.162
	(0.492)	(0.555)	(0.570)
Quarter 4	-0.412	-0.411	-0.371
	(0.516)	(0.581)	(0.629)
Health Plan Type			
Exclusive Provider Organization	-3.436***	-3.535***	-3.093***
	(0.308)	(0.354)	(0.364)
Health Maintenance Organization	-6.775***	-6.919***	-5.803***
	(0.307)	(0.342)	(0.559)
Non-capitated Point of Service (POS)	-3.508***	-3.648***	-2.776***
	(0.301)	(0.348)	(0.285)
Preferred Provider Organization	-4.923***	-5.162***	-3.611***
	(0.238)	(0.276)	(0.274)
Capitated or Partially-capitated POS	-9.680***	-9.991***	-7.466***
	(0.553)	(0.619)	(0.587)
Consumer Driven Health Plan	-7.624***	-7.955***	-5.700***
	(0.306)	(0.345)	(0.375)
High Deductible Health Plan	-7.007***	-7.310***	-5.814***
	(0.319)	(0.355)	(0.394)
Constant	22.80***	23.76***	14.93***
	(0.758)	(0.860)	(0.784)
R-squared	0.222	0.195	0.341
F-statistic	410.81***	393.06***	144.42***
Observations	27,359,428	23,785,610	3,573,818
Number of drugs	122	54	68

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable in all specifications is price per mL, adjusted for inflation. Standard errors are clustered at the drug-quarter level. All health plan coefficients should be interpreted as the change in price relative to the base health plan, comprehensive.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level

5 Results

5.1 The Effect of Pipeline Pressure on Incumbent Insulin Prices

Initial results are displayed in Table 2. All results were obtained using drug-level fixed effects linear regressions. The first column presents results obtained using the full sample, while the second and third columns stratify by insulin type, analogue or human. There are less than 30 total claims for animal insulins, making it impossible to assess effects on the pricing of insulins of this type. The direction of pipeline shock effects are similar regardless of the sample considered, though there are minor differences in magnitude and significance. Response to competitive pressure in the pipeline is stronger for insulin analogues than for human versions of insulin. The first two shocks do not have a significant effect on price. However, the third and fourth shocks significantly increase insulin price, specifically among analogues. The biggest price effect is concentrated among insulin analogues. Prices are about \$2.35 larger per mL in quarters following the third pipeline shock compared to quarters prior to this shock. The fourth pipeline shock has an additionally positive effect on price, increasing insulin price per mL by about \$2.28 in quarters following this shock. For the average patient in this sample taking 12.48 ml per month, this is an increase in the total amount paid for insulin of \$29.33 due to the third shock and an additional \$28.45 due to the final shock.

In general, price is increasing at an increasing rate over time, by about \$1.34 per quarter at the mean number of quarters since the first pipeline shock.[11] Pipeline shocks reflect a shift in this more general time trend. Since identification of the pipeline shocks relies on a correct specification of the time trend, we also consider whether there is a systematic issue in the specification of the time trend by graphing the average residuals over time, provided in Figure 7 in the Appendix. Results also indicate that there is no cyclical dimension to pricing, that is, prices in later quarters are not significantly different than prices in the first quarter of the year. Lastly, the health plan type has a considerable impact on price. All health plan types covering insulin have lower prices than comprehensive health plans, with capitated or partially-capitated POS plans, consumer driven health plans, high deductible health plans, and health maintenance organization health plans having the biggest differences in price. This may be due to in part to plan structure, but could also be due to levels of insurer bargaining power associated with each plan type. Growing literature on insurer bargaining power and bargaining power in healthcare may contribute to our understanding of these results [Ho and Lee (2017); Gaynor, Ho and Town (2015); Ho (2009); and Capps, Dranove and Satterthwaite (2003)].

[11] $\theta_1 + 2\theta_2(E(t)) = 0.715 + 2(0.0323)(9.74) = 1.344$

Table 3: The Effect of Phase 3 Pipeline News Shocks on Patient Out-of-Pocket Prices

Variable	(1) Full Sample	(2) Analogue Only	(3) Human Only
Phase 3 Shocks			
1^{st} Pipeline Shock$_t$	-0.263***	-0.274***	-0.205***
	(0.0571)	(0.0643)	(0.0739)
2^{nd} Pipeline Shock$_t$	0.142***	0.144***	0.124*
	(0.0397)	(0.0444)	(0.0750)
3^{rd} Pipeline Shock$_t$	0.161***	0.166***	0.0728
	(0.0595)	(0.0611)	(0.175)
4^{th} Pipeline Shock$_t$	0.384***	0.373***	0.472***
	(0.0604)	(0.0623)	(0.162)
Time	0.101***	0.103***	0.0907***
	(0.00541)	(0.00629)	(0.00771)
Time^2	-0.00203***	-0.00208***	-0.00204***
	(0.000309)	(0.000348)	(0.000433)
Quarter 2	-0.0705**	-0.0704**	-0.0708
	(0.0276)	(0.0302)	(0.0490)
Quarter 3	-0.172***	-0.178***	-0.136***
	(0.0264)	(0.0288)	(0.0477)
Quarter 4	-0.357***	-0.369***	-0.273***
	(0.0289)	(0.0316)	(0.0483)
Health Plan Type			
Exclusive Provider Organization	-0.636***	-0.595***	-0.807***
	(0.0519)	(0.0580)	(0.0661)
Health Maintenance Organization	-0.349***	-0.264***	-0.745***
	(0.0425)	(0.0480)	(0.0833)
Non-capitated Point of Service (POS)	-0.0206	-0.00263	-0.0210
	(0.0343)	(0.0402)	(0.0487)
Preferred Provider Organization	0.0387	0.0811	-0.159***
	(0.0431)	(0.0507)	(0.0479)
Capitated or Partially-capitated POS	-0.597***	-0.604***	-0.336***
	(0.0520)	(0.0585)	(0.0837)
Consumer Driven Health Plan	-0.773***	-0.701***	-1.277***
	(0.0721)	(0.0814)	(0.0734)
High Deductible Health Plan	-0.981***	-0.903***	-1.624***
	(0.0813)	(0.0906)	(0.0813)
Constant	2.731***	2.719***	2.682***
	(0.0577)	(0.0652)	(0.0814)
R-squared	0.062	0.055	0.101
F-statistic	295.21***	295.38***	191.65***
Number of drugs	122	54	68
Observations	27,359,428	23,785,610	3,573,818

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable in all specifications is patient price per mL which includes all patient out-of-pocket costs, adjusted for inflation. Standard errors are clustered at the drug-quarter level. All health plan coefficients should be interpreted as the change in patient out-of-pocket costs relative to the base health plan, comprehensive.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level

Table 3 provides estimates of the effect of pipeline news shocks on patient out-of-pocket costs. Pipeline shocks have largely significant effects on patient prices, as price changes are passed on to consumers. All but one of these pipeline shocks, the first, has a positive effect on price. The second, third, and fourth pipeline shocks are associated with price increases of \$0.14, \$0.16, and \$0.38, respectively, in quarters after the shocks. All of these price effects are statistically significant at the one percent level, but significant responses are mostly concentrated among insulin analogues. For the average patient in this sample taking 12.48 ml per month, this is an increase in out-of-pocket costs for insulin of \$1.74, \$2.00, and \$4.74, respectively, or a total of \$26.48 additional out-of-pocket costs over 8 years due to competition pressure from the pipeline. On average, that's an additional \$3.31 per year.

The first pipeline shock decreases patient price following the shock by about \$0.26. This result is also statistically significant at the one percent level. This suggests that there may be something different about the first pipeline shock. This market information shock represents Afrezza completing the last phase of drug development has a significantly negative effect on price, but the rest of the pipeline shocks increase price. This is likely due to the degree of product differentiation associated with Afrezza. Afrezza is an inhale-able insulin, while the rest of the drugs on the market are injectables. This pipeline shock decreases out-of-pocket costs by about \$3.24 for the average patient in this sample, bringing the total change in patient costs due to pipeline pressure to an increase of about \$23.24 over 8 years. This also demonstrates that incumbent manufacturers may have a holistic view of the probability of entry as indicated by information from the pipeline. As more than one potential competitor completes phase 3, the probability that one of them will eventually be successful increases. As demonstrated in the theory, manufacturers will increase price when facing relatively inelastic demand in a setting where entry is becoming more likely.

Trends in patient prices are somewhat different than trends for total prices. Patient out-of-pocket costs are lower for only a few plan types relative to comprehensive plans. This includes EPOs, HMOs, Capitated or Partially-capitated POS, CDHPs, and HDHPs. High deductible plans are associated with the biggest reduction in patient prices relative to comprehensive plans, which may demonstrate that patients in high-deductible plans are much more price sensitive than patients in other health plans. In addition, note that quarter of the year effects have considerably significant effect on patient out-of-pocket costs. Patient prices are significantly lower in the second, third, and fourth quarters relative to the first quarter of the year, and patient out-of-pocket costs are lowest in the fourth quarter relative to the first quarter. This likely reflects the decline in out-of-pocket costs as patients hit their deductible during the year.

5.1.1 Verifying Shock Exogeneity: Restricting the Analysis to External Firm Shocks

Incumbent insulins in our sample are only manufactured by three drug companies, Sanofi, Novo Nordisk, and Eli Lilly. Each of these firms also has another insulin in development during our panel that clears various phases of the drug development pipeline. In this market, an incumbent firm with a product in one category of insulin may be in drug development for a different insulin in another category. We will consider the issue of category and the definition of the market in detail in a later section. For now, let us only consider the effect this may have on the exogeneity of the pipeline shocks. For a firm with both an incumbent drug and a new drug in the development pipeline, the information about success in the pipeline will not necessarily be a "shock" to this incumbent at all. Firms may internalize their success in the drug development pipeline as they anticipate pricing effects from their new drug. Therefore, we also conduct firm-specific pipeline shock tests. While it is reasonable to assume that external pipeline shocks, across firms, are exogenous, it is may be inappropriate to assume that internal pipeline shocks, within firm, are exogenous. Therefore, we stratify our sample at the firm-level, and consider only the shocks that are external to the firm. In other words, we drop pipeline shocks from a firm's own drug.

Table 4 presents results from firm-specific shock tests. Note that qualitatively, the impact of each shock is qualitatively similar both in the full sample without regard to strict shock exogeneity and by firm, excluding shocks which may be internalized. However, it is striking to note that Eli Lilly and Sanofi prices changes, drive the results in the full sample. Eli Lilly increases prices by about \$4.19 in quarters following the fourth shock, and Sanofi increases prices by about \$4.47 in quarters following the third shock. These effects are only somewhat significant, at the ten and five percent levels, respectively. There is no significant change in prices among Novo Nordisks insulin products in response to any of the pipeline shocks. It is worth considering how each of these firms may view these pipeline shocks. The amount of competitive pressure associated with pipeline shocks will likely depend on the degree to which these products are used as perfect and/or imperfect substitutes in practice and whether or not they can also be used in complementary ways. Section 5.2 details particular categories of these drugs to highlight the nature of competition in these markets.

5.1.2 Differential Effects by Plan Design – Copayment or Coinsurance

As discussed in the theoretical model presented previously, patients facing copayment for prescription drugs tend to be less price sensitive than those facing coinsurance. In the insulin market considered here, 74.9 percent of claims for insulin require a copayment only. 16.7 percent of claims have no patient out-of-

Table 4: Verifying Shock Exogeneity: Firm-specific Shock Tests

Variable	(1) Full Sample	(2) Eli Lilly	(3) Sanofi	(4) Novo Nordisk
Phase 3 Shocks				
1^{st} Pipeline Shock$_t$	-0.726	-0.109	-1.567	0.609
	(0.795)	(1.437)	(0.950)	(1.538)
2^{nd} Pipeline Shock$_t$	-1.147	-1.726	-1.112	
	(0.912)	(1.065)	(1.681)	
3^{rd} Pipeline Shock$_t$	2.285**		4.467**	1.936
	(1.053)		(1.723)	(1.460)
4^{th} Pipeline Shock$_t$	2.263**	4.192*		1.522
	(1.142)	(2.167)		(1.638)
Time	0.715***	0.668***	0.833***	0.466***
	(0.0957)	(0.164)	(0.141)	(0.164)
Time^2	0.0323***	0.0435***	0.0267***	0.0376***
	(0.00636)	(0.00901)	(0.00801)	(0.00927)
Quarter 2	-0.643	-0.824	-0.408	-0.458
	(0.455)	(0.777)	(0.740)	(0.714)
Quarter 3	-0.278	-0.0705	-0.283	-0.178
	(0.492)	(0.839)	(0.810)	(0.749)
Quarter 4	-0.412	-0.120	-0.687	-0.181
	(0.516)	(0.855)	(0.868)	(0.782)
Health Plan Type				
Exclusive Provider Organization	-3.436***	-4.266***	-4.248***	-1.326*
	(0.308)	(0.513)	(0.394)	(0.698)
Health Maintenance Organization	-6.775***	-9.832***	-7.144***	-3.591***
	(0.307)	(0.575)	(0.487)	(0.542)
Non-capitated Point of Service (POS)	-3.508***	-3.589***	-4.506***	-1.678***
	(0.301)	(0.429)	(0.510)	(0.539)
Preferred Provider Organization	-4.923***	-5.972***	-5.878***	-2.387***
	(0.238)	(0.366)	(0.319)	(0.529)
Capitated or Partially-capitated POS	-9.680***	-10.36***	-10.73***	-7.267***
	(0.553)	(0.720)	(1.058)	(0.812)
Consumer Driven Health Plan	-7.624***	-8.043***	-8.479***	-5.903***
	(0.306)	(0.536)	(0.490)	(0.541)
High Deductible Health Plan	-7.007***	-7.472***	-8.466***	-4.347***
	(0.319)	(0.518)	(0.422)	(0.604)
Constant	22.80***	25.69***	21.38***	21.04***
	(0.758)	(1.307)	(1.068)	(1.353)
R-squared	0.222	0.274	0.178	0.212
F-statistic	410.81***	201.25***	254.20***	209.75***
Observations	27,359,428	7,215,129	11,299,605	8,834,609
Number of drugs	122	40	7	31

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable in all columns is the price per mL, adjusted for inflation. Firm-stratification is provided in the column heading. Standard errors are clustered at the drug-quarter level.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level

Table 5: Differential Effects: Copayment or Coinsurance

Variable	(1) Price	(2) Patient Out-of-Pocket	(3) Price	(4) Patient Out-of-Pocket
	Copayment Only		Coinsurance Only	
Phase 3 Shocks				
1^{st} Pipeline Shock$_t$	-0.640	-0.226***	-0.342	-0.513***
	(0.807)	(0.0488)	(1.004)	(0.165)
2^{nd} Pipeline Shock$_t$	-1.223	-0.0810*	-1.934**	0.202**
	(0.952)	(0.0421)	(0.917)	(0.100)
3^{rd} Pipeline Shock$_t$	2.103*	0.0906	4.374***	0.0570
	(1.154)	(0.0641)	(0.811)	(0.103)
4^{th} Pipeline Shock$_t$	2.376*	0.381***	3.831***	0.457***
	(1.281)	(0.0708)	(0.866)	(0.115)
Time	0.797***	0.108***	0.561***	0.227***
	(0.0970)	(0.00485)	(0.109)	(0.0152)
Time^2	0.0300***	-0.00137***	0.0148***	-0.00202***
	(0.00651)	(0.000312)	(0.00517)	(0.000683)
Quarter 2	-0.896*	-0.0610**	-0.404	-0.0170
	(0.476)	(0.0264)	(0.551)	(0.0761)
Quarter 3	-0.504	-0.0612**	-0.410	0.0847
	(0.505)	(0.0271)	(0.543)	(0.0685)
Quarter 4	-0.651	-0.156***	-0.840	-0.144**
	(0.534)	(0.0279)	(0.527)	(0.0697)
Health Plan Type				
Exclusive Provider Organization	-4.329***	-1.255***	-1.485*	1.574***
	(0.280)	(0.0579)	(0.774)	(0.149)
Health Maintenance Organization	-7.620***	-0.748***	-5.041***	2.719***
	(0.292)	(0.0399)	(0.644)	(0.152)
Non-capitated Point of Service (POS)	-4.234***	-0.443***	-5.532***	0.662***
	(0.264)	(0.0346)	(0.659)	(0.0747)
Preferred Provider Organization	-4.678***	-0.194***	-1.833**	0.881***
	(0.221)	(0.0278)	(0.722)	(0.0720)
Capitated or Partially-capitated POS	-10.04***	-0.912***	-4.653***	0.321**
	(0.504)	(0.0575)	(0.801)	(0.149)
Consumer Driven Health Plan	-8.173***	0.522***	-5.375***	0.741***
	(0.288)	(0.0632)	(0.767)	(0.0838)
High Deductible Health Plan	-5.347***	-0.0595	-0.745	0.561***
	(0.341)	(0.0571)	(0.798)	(0.102)
Constant	23.62***	3.267***	22.37***	2.345***
	(0.768)	(0.0508)	(1.019)	(0.118)
R-squared	0.234	0.093	0.177	0.167
F-statistic	299.51***	368.12***	159.93***	335.91***
Observations	20,520,743	20,520,743	2,317,705	2,317,705
Number of drugs	117	117	97	97

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable is provided in the column heading. All prices are inflation adjusted and given in constant 2010 US Dollars. Standard errors are clustered at the drug-quarter level.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level

pocket costs,[12] neither copay nor coinsurance. The remaining 8.4 percent of claims is comprised mostly of payments with coinsurance only (8.2 percent) and a combination of copayment and coinsurance (0.2 percent). Therefore, it is reasonable to expect less price sensitivity from consumers covered by a plan with tiered copays instead of coinsurance. In this case, it may be advantageous to manufacturers to offer lower prices to plans with coinsurance than those with copayments. We conduct another specification, allowing prices to differ according to the structure of patient out-of-pocket costs. This will effectively serve as a proxy to group patients by their price elasticity.

In general, the effect of pipeline shocks on both price and patient out-of-pocket costs is qualitatively similar for both claims requiring a copayment and claims requiring coinsurance. However, the size and significance of pipeline shock effects is larger and more significant for claims with coinsurance compared to claims with copayment. This result is surprising, given that we postulated that patients under coinsurance would be more price sensitive than those facing copayment. The positive effect on price from the third shock is approximately $2.27 more among claims with coinsurance, and the positive effect on price from the fourth shock is about $1.45 more among coinsurance claims. Manufacturers may offer bigger discounts and/or different rebates for certain plans with copayment since they comprise a larger part of the market. Unfortunately, drug-level rebates are proprietary and the size of discounts cannot be assessed with claims data. This could also reflect a larger degree of bargaining power for the manufacturer compared to the insurer among plans with coinsurance. Without additional data on these contractural arrangements, it is unclear what may be driving this difference.

5.2 The Effect of Pipeline News on Insulin Prices by Category

The preliminary market definition is quite wide, and assumes that all insulin drugs compete with one another. A narrow market definition would specify that insulin products only compete with one another within category. We classify drugs into three market categories − bolus, basal, and mixed. This terminology is derived from the medical terminology which indicates how an insulin is absorbed and metabolized by the body. These categories are defined by three factors, onset, peak, and duration, of the drug. Bolus insulins tend to have a quick onset, moderate peaks, and moderate durations. Basal insulins tend to have slow onset, longer peaks, and longer durations. Mixed insulins typically contain both a bolus and basal insulin, and have a quick onset, long peak, and long duration. These characteristics of incumbent and potential entrant drugs are presented in Table 6. A range is provided because each drug formulation is absorbed

[12]The majority of these claims are for older versions of insulin provided at low costs.

Table 6: Narrow Market Definition

Category	Onset	Peak	Duration
Bolus	≈ 0.5 hrs or less	$0.5 - 3.5$ hrs	$2 - 8$ hrs
Basal	$1 - 6$ hrs	$4 - 12$ hrs or No Peak	$7 - 24$ hrs or more
Mix	≈ 0.5 hrs or less	$0.5 - 12$ hrs	$18 - 24$ hrs or more
Category	Incumbent Drugs		Entrant Drugs
Bolus	**Apidra, Humalog, Novolog, Humulin R, Novolin R**		Afrezza
Basal	**Lantus, Levemir, Humulin N, Novolin N**		Basaglar, Toujeo, Tresiba
Mix	**Humalog** $^{50}/_{50}$ **and** $^{75}/_{25}$**, Novolog** $^{70}/_{30}$**,** Humulin $^{70}/_{30}$, **Novolin** $^{70}/_{30}$		Ryzodeg $^{70}/_{30}$

Note. Drugs listed in **bold text** are incumbent insulins.

somewhat differently, both between drugs and by different patients. For example, Humalog and Apidra insulins have somewhat different peak, onsets, and durations, even though they are both used as "bolus" insulins. Similarly, one patient may experience a rapid-acting insulin peak at one hour while another patient experiences the peak at 1.5 hours using the same drug.

Within category, insulins can usually be substituted, with the caveat that counseling/education may be needed to help assure adequate glucose coverage and safety in the transition. Between categories, it's difficult to specify the degree of substitutability as it may depend on an individual patient's insulin sensitivity or resistance as well as an individual patient's treatment therapy. Therefore, it is possible that manufacturers only see potential competitors "within category" as a competitive threat. Insulins "between categories" are often used in complementary ways. For example, consider these two treatment options. A patient can use long-acting insulin to provide basal glucose control in conjunction with a rapid-acting insulin to provide bolus control. A patient can also use only rapid-acting insulin delivered in small increments throughout the day to provide both basal and bolus control. Both treatment options can achieve the treatment goal of glucose control. Figure 6 demonstrates that 61.81 percent of patients in the sample fill a prescription for both a basal and bolus insulin, suggesting the majority of patients use these between category drugs as complements.[13]

Phase 3 pipeline shocks were constructed similarly in this specification. Because only one bolus insulin and one mix insulin were in the clinical trials phase of the drug development pipeline over this time frame,

[13]See Table 10 in the Appendix for number of claims.

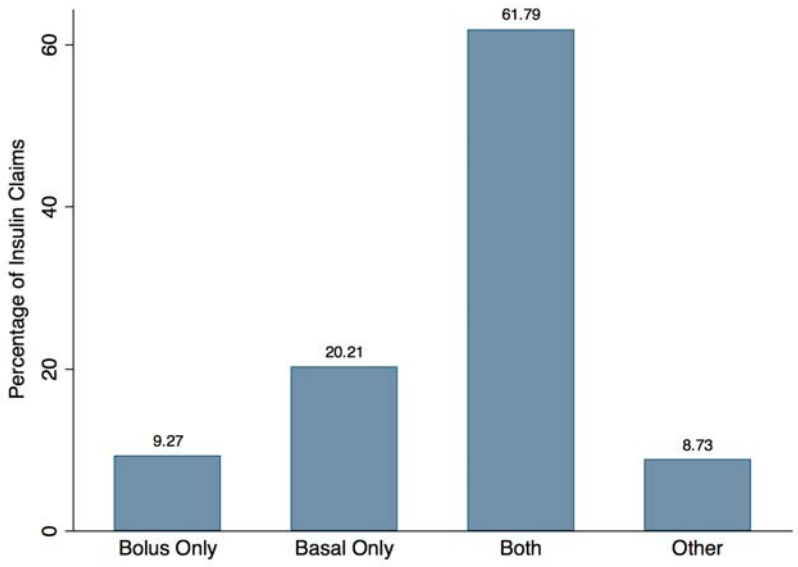

Figure 6: Insulin Treatment Combinations

there is only one pipeline shock in each of these categories. There were three phase 3 pipeline shocks in the basal category. Results from this specification are provided in Table 7. Note that the majority of the large and significant effects are isolated in the basal category. This matches the theory where we see that an increase in the probability of entry can drive escalating prices. Since the basal insulin category is the only category in which more than one potential entrant successfully clears phase 3 of drug development, it may be the only category where incumbent manufacturers have a large degree of confidence that probability of entry is likely. This specification also reveals that the specifics of the shock may matter substantially. The driving shock in the basal category is the Basaglar shock.

5.3 Other Robustness Checks

We test whether our results are robust to several other confounders that may affect the pricing decision. Regardless of how these factors affect the pricing decision, it is unlikely that these factors are timed exactly to the timing of drug development phase clearance. Therefore, we are not generally concerned about whether the omission of these factors misidentifies the pipeline shocks. However, we run robustness checks for a number of potential concerns. First, we control for supplemental indications for incumbent drugs, which may increase price. Supplemental indications typically expand the number of patients that can be treated with the drug by shifting the demand curve to the right. These supplemental indications also significantly increase drug price, but previous estimates of the effect of pipeline shocks are robust to this specification.

Table 7: Phase 3 Pipeline Shocks and Competition within Category

Variable	(1) Price	(2) Patient Out-of-Pocket
Bolus Category		
Afrezza Pipeline Shock$_t$	1.899	-0.277***
	(1.455)	(0.0876)
Observations	9,909,100	9,909,100
Number of drugs	45	45
Basal Category		
Tresiba Pipeline Shock$_t$	-0.521	0.173***
	(1.320)	(0.0629)
Basaglar Pipeline Shock$_t$	3.330**	0.168*
	(1.448)	(0.0912)
Toujeo Pipeline Shock$_t$	2.222	0.395***
	(1.652)	(0.0868)
Observations	14,561,425	14,561,425
Number of drugs	41	41
Mix Category		
Ryzodeg $\frac{70}{30}$ Pipeline Shock$_t$	-1.712***	0.0984*
	(0.514)	(0.0523)
Observations	2,888,902	2,888,902
Number of drugs	35	35

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable is provided in the column heading. Standard errors are clustered at the drug-quarter level. All regressions include health plan indicators, time trends and quarter binaries.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level

Second, we test whether the passage of the BPCI in 2010 had a significant affect on price. Previous results are also robust to this specification. Third, mail-order discounts, often for a 90-day supply, may also play a role in pricing. To test for the robustness of the price effects of pipeline shocks, we also account for whether a prescription was filled for 90 days or for 30 days. Price effects due to pipeline shocks are robust to this as well. Fourth, estimated price effects are also robust to using the medical consumer price index to adjust prices for inflation. Fifth, we also test a specification in which time trends differ at the brand-level to account for differing within-brand pricing strategy trends. Price effects of pipeline shocks are robust to this robustness check as well.

Sixth, we also consider whether pipeline shocks from earlier phases have similar effects. As previously mentioned, the vast amount of uncertainty associated with drug development likely reduces the information that an existing competitor can glean about potential competition from earlier phases. Price effects from phase 3 pipeline shocks are robust to including pipeline shocks from phase 2 and phase 1. In addition, there are no significant price effects from phase 2 or phase 1 pipeline shocks. Seventh, we evaluate whether results are driven by outliers. Previous results are also robust to excluding outliers from the analysis, and nearly identical in both magnitude and significance. An alternative approach to considering the role of outliers would be to consider whether price responses at the median are the same as those on average, using quintile regressions with fixed effects as illustrated in Powell (2014) and Powell and Wagner (2014). Unfortunately, these methods are developed for panel data, and would require collapsing claims-level data into drug-level panel data, loosing a considerable amount of price variation. Since results are robust to the exclusion of outliers, it is unlikely that this approach will be informative. Lastly, we assess the role of Affordable Care Act (ACA) demand expansion on these price increases. Recent work by Berndt, Conti and Murphy (2017) finds both a reduction in the number of generic drug suppliers and an increase in the price of generic drugs following the implementation of the ACA. To consider this effect, we reframe time trends to include a pre-ACA and post-ACA time trend. Using pre- and post-ACA trends magnifies the size and significance of all the pipeline shocks except for the third shock. The price effect from the third shock becomes insignificant, though remains positive. The first and final shock increase price by \$2.40 and \$3.43, respectively, and are both significant at the one percent level in this specification. Results from this specification are presented in Table 11 in the Appendix.

5.4 Limitations

Despite rigorous considerations of these issues, there are other factors that may influence pricing strategies that are either not observed or not considered in our empirical analysis. Drug-level rebate size and formulary tier status, negotiated between manufacturers and payers using pharmacy benefit managers (PBMs), are key unobservables. If manufacturers truly compete over the size of the rebates to receive favorable status on formulary tiers, and not over the payments or list price of their products, then this analysis may not correctly measure the competitive effects of new branded drugs in the pipeline. Unfortunately, this information is proprietary and it is not possible to estimate drug-level measures for either of these unobservables. The database used in the analysis contains claims from over 100 payers, making it infeasible to obtain formulary tier status or rebates at the drug-level. It may be possible to back out manufacturer-level rebate sizes, but this will do little to assess the impact of rebate size or formulary status on the pricing decision. One factor that is observable but not included in the analysis is research and development (R&D) costs. Though research and development costs can be observed at the firm level and an approximate per drug R&D cost can be estimated as in DiMasi, Grabowski and Hansen (2016), there is no way to isolate a drug-specific R&D cost. In addition, it is unlikely to bias estimates on the effect of pipeline pressure. Research and development costs are sunk costs and should not be considered in the pricing decision. However, research and development costs do create a significant barrier to potential entry which thereby impacts competition and the pricing decision. Therefore, these may both be limitations of the analysis, and therefore suggest important areas of further research.

5.5 Policy Implications for Biosimilar Drugs

Our results suggest that potential biosimilar entry may be perceived differently than other branded therapeutic substitutes. Understanding the implications for these differences requires additional institutional details. The pricing of large molecule drugs, or biologics, like insulin may differ from pricing decisions for small molecule drugs. A biologic is a pharmaceutical drug product manufactured in, extracted from, or semi-synthesized from biological sources. These large molecule drugs are more difficult to replicate, reducing the likelihood that biosimilar entry will occur. According to the FDA, "a biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product," where the reference product is a biologic already approved by the FDA. A biosimilar must demonstrate that both its structure and function are similar to the reference product. It must also demonstrate that there are "no clinically meaningful differences from the reference product in terms of safety, purity, and

potency (safety and efficacy)." For a biosimilar to be deemed "interchangeable" with a reference product, it must meet additional requirements. Biosimilars are approved through a different abbreviated pathway that avoids duplicating costly clinical trials. However, prior to 2010, there was no regulatory pathway for biosimilar approval. The Biologics Price Competition and Innovation (BPCI) Act of 2009 was signed into law on March 23, 2010.

However, Basaglar is *not* approved as a biosimilar product. It was approved through an abbreviated pathway after submitting a 505(b)(2) application (Food and Drug Administration 2015). This application relied on comparisons of Basaglar and Lantus, a previously FDA-approved basal insulin, and FDA findings of safety and effectiveness for Lantus, or insulin glargine. According to the FDA, there is no insulin glargine "reference product" under license with the Public Health Service Act. It is not clear whether the manufacturer for Eli Lilly submitted a 505(b)(2) application because of this, or because studies for Basaglar began prior to the BPCI approval. In addition, Basaglar's FDA approval was delayed, due to a lawsuit filed by the manufacturer of Lantus, which alleged numerous patent infringements.[14] On the other hand, Basaglar is considered a biosimilar by several European drug approval agencies. For these reasons, it would be reasonable for an existing drug manufacturer to consider this product a biosimilar as it conducted clinical trials in the pipeline. Therefore, it may also be reasonable to generalize our results as a typical response of incumbents to potential biosimilar entry.

These details highlight two important issues that inform the outlook for drug pricing with the entry of biosimilars. First, there may considerable legal battles over patent infringement for the entry of many biosimilars, which will likely encourage additional upward pressure on price. Pharmaceutical companies, both incumbents and entrants, will be incentivized to cover costs associated with funding these lawsuits by raising price. Second, it is unclear whether drug manufacturers will pursue biosimilar entry or pursue alternative abbreviated pathways, such as the 505(b)(2). Basaglar did not conduct phase 2 clinical trials, as illustrated in Table 8. If other abbreviated pathways can cut the costs of R&D, it may be more advantageous to pursue those pathways. Finally, biosimilar entry may not be profitable if the market is saturated by enough branded biologic substitutes. It is still too early to assess whether there will be a large degree of biosimilar entry, actual or potential, and whether that competition will be *enough* to exert downward pressure on price. Our results seem to suggest that given the institutional structure, potential biosimilar entry or other follow-on entry could encourage incumbent drugs to increase price. However, this would require significant reconsideration, as our model demonstrating this price increase incentive is partially driven by the share

[14]Sanofi-Aventis US LLC et al v. Eli Lilly and Co, U.S. District Court, District of Delaware, No. 14-00884

θ that switch to the new product. In the case of a biosimilar that is "interchangeable" with a reference product, a patient may be switched to the biosimiliar in part *due to price*. In this case, the market share loss following biosimilar entry may be greater than we assess, possibly off-setting the potential revenue gains from increasing price in the first period. For the curious reader, our model could be extended to structure θ as a function of price or copayment which could help assess the competitive effects of biosimilar entry.

6 Conclusion

In this study, we demonstrate both a strategic incentive for incumbent firms under patent to raise drug prices as the likelihood of competition from another brand name patented drug increases, both theoretically and empirically. Results suggest that pipeline pressure significantly increases the prices of incumbent drugs, and potential biosimilar entry may drive this effect. Specifically, prices for insulin increase by around $30 per patient for each of the later pipeline shocks in our analysis. However, this incentive explains a little less than 10 percent of the price increases observed from 2007-2015. Therefore, there is considerable work to be done to assess the role of manufacturer-insurer bargaining power, and other important market characteristics like drug rebates and formulary tier status that likely play a role in increasing prices. Future work should also consider the differential welfare impact on patients with high deductibles and larger out-of-pocket costs and patients without insurance.

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A Appendix

A.1 Derivations and Proofs

The following solution describes the steps used to obtain the entrant's best response function in Equation 4.

$$
\begin{aligned}
FOCP_{2e}: \frac{\partial R_e}{\partial P_{2e}} = \left[a - b_1 c_{2e} + b_2 c_{2i}\right] + P_{2e} \cdot -b_1 \frac{c_{2e}}{P_{2e}} &= 0 \\
a - b_1 c_{2e} + b_2 c_{2i} - P_{2e} \cdot b_1 \frac{c_{1i}}{P_{1i}} &= 0 \text{ (Using Lemma ?? and Assumption 4)} \\
a - b_1 \left(\frac{c_{1i}}{P_{1i}} P_{2e}\right) + b_2 c_{2i} - b_1 \frac{c_{1i}}{P_{1i}} P_{2e} &= 0 \text{ (Using } c_{2e} = \frac{c_{1i}}{P_{1i}} P_{2e} \text{)} \\
\theta Q + c_{2i}(b_1 - b_2) - 2b_1 \frac{c_{1i}}{P_{1i}} P_{2e} + b_2 c_{2i} &= 0 \text{ (Replacing a from 2)} \\
\theta Q + \frac{c_{1i}}{P_{1i}} P_{2i}(b_1 - b_2) - 2b_1 \frac{c_{1i}}{P_{1i}} P_{2e} + b_2 \frac{c_{1i}}{P_{1i}} P_{2i} &= 0 \text{ (Using } c_{2i} = \frac{c_{1i}}{P_{1i}} P_{2i} \text{)} \\
\theta Q + b_1 \frac{c_{1i}}{P_{1i}} P_{2i} - 2b_1 \frac{c_{1i}}{P_{1i}} P_{2e} &= 0 \text{ (Simplifying)} \\
\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i} &= P_{2e} \text{ (Solving for } P_{2e}) \\
P_{2e} = \frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i} & \qquad (17)
\end{aligned}
$$

The following solution describes the steps used to obtain the incumbent's simplified second period maximization problem in Equation 9.

$$
\begin{aligned}
\max P_{2i} \cdot Q_{2i} &= P_{2i} \cdot \left[\alpha - \beta_1 c_{2i} + \beta_2 c_{2e}\right] \\
&= P_{2i} \cdot \left[\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} P_{2e}\right] \text{ (Using } c_{2i} = \frac{c_{1i}}{P_{1i}} P_{2i} \text{ and } c_{2e} = \frac{c_{1i}}{P_{1i}} P_{2e} \text{)} \\
&= P_{2i} \cdot \left[\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} \left(\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i}\right)\right] \text{ (Using the entrant's best response from Equation ??)} \\
&= P_{2i} \cdot \left[\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} \left(\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i}\right)\right] \text{ (Simplifying)}
\end{aligned}
$$

The following solution describes the steps used to obtain the incumbent's best response function in Equation 11.

$$
\begin{aligned}
FOCP_{2i} : \frac{\partial R_i}{\partial P_{2i}} = \Big[\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} \Big(\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i} \Big) \Big] + \\
P_{2i} \cdot \Big[- \beta_1 \frac{c_{1i}}{P_{1i}} + \beta_2 \frac{c_{1i}}{P_{1i}} \Big(\frac{1}{2} \Big) \Big] = 0 \\
\alpha - 2\beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{\theta Q}{2 b_1} + \beta_2 \frac{c_{1i}}{P_{1i}} P_{2i} = 0 \text{ (Simplifying)} \\
\alpha + \beta_2 \frac{\theta Q}{2 b_1} = 2\beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} - \beta_2 \frac{c_{1i}}{P_{1i}} P_{2i} \\
\alpha + \beta_2 \frac{\theta Q}{2 b_1} = \frac{c_{1i}}{P_{1i}} (2\beta_1 - \beta_2) P_{2i} \\
P_{1i} \frac{\alpha + \beta_2 \frac{\theta Q}{2 b_1}}{c_{1i}(2\beta_1 - \beta_2)} = P_{2i}
\end{aligned}
$$

$$
P_{2i} = P_{1i} \frac{\alpha + \beta_2 \frac{\theta Q}{2 b_1}}{c_{1i}(2\beta_1 - \beta_2)} \tag{18}
$$

The following solution describes the steps used to obtain a simplified version of the incumbent's two period decision problem in Equation 12

$$
\begin{aligned}
\max_{P_{1i}} R_i &= P_{1i} \cdot Q_{1i} + \big[(1-\rho) P_{1i} \cdot Q_{1i} + \rho P_{2i} \cdot Q_{2i} \big] \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho P_{2i} (\alpha - \beta_1 c_{2i} + \beta_2 c_{2e}) \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho\omega \frac{P_{1i}}{c_{1i}} (\alpha - \beta_1 c_{2i} + \beta_2 c_{2e}) \\
&\text{(Replacing } P_{2i} = \omega \frac{P_{1i}}{c_{1i}}\text{)} \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho\omega \frac{P_{1i}}{c_{1i}} \Big(\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} P_{2e} \Big) \\
&\text{(Using } c_{2i} = \frac{c_{1i}}{P_{1i}} P_{2i} \text{ and } c_{2e} = \frac{c_{1i}}{P_{1i}} P_{2e}\text{)} \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho\omega \frac{P_{1i}}{c_{1i}} \Big(\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} P_{2i} + \beta_2 \frac{c_{1i}}{P_{1i}} \Big[\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} P_{2i} \Big] \Big) \\
&\text{(Using the Entrant's BR)} \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho\omega \frac{P_{1i}}{c_{1i}} \Big(\alpha - \beta_1 \frac{c_{1i}}{P_{1i}} \omega \frac{P_{1i}}{c_{1i}} + \beta_2 \frac{c_{1i}}{P_{1i}} \Big[\frac{\theta Q P_{1i}}{2 b_1 c_{1i}} + \frac{1}{2} \omega \frac{P_{1i}}{c_{1i}} \Big] \Big) \\
&\text{(Using } P_{2i} = \omega \frac{P_{1i}}{c_{1i}}\text{)} \\
&= P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + (1-\rho) P_{1i} \cdot (\alpha - \beta_1 \cdot c_{1i}) + \rho\omega \frac{P_{1i}}{c_{1i}} \Big(\alpha - \beta_1 \omega + \beta_2 \Big[\frac{\theta Q}{2 b_1} + \frac{1}{2} \omega \Big] \Big) \\
&\text{(Simplifying)}
\end{aligned}
$$

The following solution describes the steps used to obtain Equation 14.

$$
\begin{aligned}
FOC_{P_{1i}} : \frac{\partial R_i}{\partial P_{1i}} = \ & (\alpha - \beta_1 c_{1i}) + P_{1i}\Big(- \beta_1 \frac{c_{1i}}{P_{1i}}\Big) + (1-\rho)\Big[(\alpha - \beta_1 c_{1i}) + P_{1i}\Big(- \beta_1 \frac{c_{1i}}{P_{1i}}\Big)\Big] \\
& + \rho\omega\Big(\alpha - \beta_1\omega + \beta_2\Big[\frac{\theta Q}{2b_1} + \frac{1}{2}\omega\Big]\Big)\Big(\frac{c_{1i} - P_{1i}\frac{c_{1i}}{P_{1i}}}{c_{1i}^2}\Big) = 0 \\
\alpha - 2\beta_1 c_{1i} + (1-\rho)(\alpha - 2\beta_1 c_{1i}) + \rho\omega\Big(\alpha - \beta_1\omega + \beta_2\Big[\frac{\theta Q}{2b_1} + \frac{1}{2}\omega\Big]\Big)\Big(\frac{0}{c_{1i}^2}\Big) = 0 \\
\alpha - 2\beta_1 c_{1i} + (1-\rho)(\alpha - 2\beta_1 c_{1i}) = 0 \\
2\alpha - 4\beta_1 c_{1i} - \alpha\rho + \rho 2\beta_1 c_{1i} = 0
\end{aligned}
$$

The following solution describes the steps using implicit function differentiation to derive the condition presented in Equation 15.

$$
\frac{\mathrm{d}P_{1i}}{\mathrm{d}\rho} = \frac{-4\beta_1\frac{c_{1i}}{P_{1i}} + \rho 2\beta_1\frac{c_{1i}}{P_{1i}}}{-\alpha + 2\beta_1 c_{1i}} = \frac{2\beta_1\frac{c_{1i}}{P_{1i}}(\rho - 2)}{2\beta_1 c_{1i} - \alpha}
$$

The following solution describes the method used to solve for a range of elasticities for which the incumbent has an incentive to increase price prior to entry.

$$
\begin{aligned}
\varepsilon = \frac{\beta_1 c_{1i}}{\alpha - \beta_1 c_{1i}} &< y \\
\beta_1 c_{1i} &< y(\alpha - \beta_1 c_{1i}) \\
(y+1)\beta_1 c_{1i} &< y\alpha \\
\frac{y+1}{y}\beta_1 c_{1i} - \alpha &< 0
\end{aligned}
$$

To find the range of elasticities for which $2\beta_1 c_{1i} - \alpha < 0$, simply solve for y by setting $\frac{y+1}{y} = 2$. This inequality will be satisfied when $\varepsilon = 1$. In fact, it will be satisfied as long as $|\varepsilon| \leq 1$.

Table 8: Clinical Trial Details for Drugs in Development

Brand Name	Trial Label from Med Review	NCT ID	Phase	Study Start
Afrezza	PDC-INS-0002	NCT00511979	1	Aug-99
Afrezza	MKC-TI-015	NCT01021891	1	Jul-06
Afrezza	MKC-TI-017	NCT00626249	1	Aug-07
Afrezza		NCT00642538	1	Feb-08
Afrezza	MKC-TI-131	NCT00721344	1	Apr-08
Afrezza	MKC-TI-113	NCT00673621	1	May-08
Afrezza	MKC-TI-114	NCT00674050	1	May-08
Afrezza	MKC-TI-122	NCT00757367	1	Jul-08
Afrezza	MKC-TI-167	NCT01365117	1	Jan-11
Afrezza	MKC-TI-176	NCT01490762	1	Dec-11
Afrezza	MKC-TI-177	NCT01544881	1	Mar-12
Afrezza	MKC-TI-178	NCT01902121	1	Aug-13
Afrezza	MKC-TI-179	NCT01982604	1	Nov-13
Afrezza		NCT02470637	1	Jun-15
Afrezza		NCT02485327	1	Jul-15
Afrezza	MKC-TI-138		1	
Afrezza	**MKC-TI-03B**	**NCT00419302**	**2**	**Oct-03**
Afrezza	PDC-INS-0008	NCT00511602	2	Dec-03
Afrezza	MKC-TI-003B2	NCT00511719	2	Feb-04
Afrezza	MKC-TI-010	NCT00754624	2	May-04
Afrezza	MKC-TI-005	NCT00511732	2	Jun-04
Afrezza	MKC-TI-016	NCT00934414	2	Aug-04
Afrezza	MKC-TI-101	NCT00539396	2	Mar-05
Afrezza	MKC-TI-118	NCT00570687	2	Sep-07
Afrezza	MKC-TI-112	NCT00642681	2	Dec-07
Afrezza	MKC-TI-116	NCT00662857	2	Apr-08
Afrezza	MKC-TI-119	NCT00747006	2	Sep-08
Afrezza	MKC-TI-026		2	
Afrezza	**MKC-TI-103**	**NCT00332488**	**3**	**Dec-04**
Afrezza	MKC-TI-030	NCT00308737	3	Jun-05
Afrezza	MKC-TI-014	NCT00539890	3	Nov-05
Afrezza	MKC-TI-009	NCT00308308	3	Feb-06
Afrezza	MKC-TI-102	NCT00309244	3	Feb-06
Afrezza	MKC-TI-105	NCT00332826	3	Jun-06
Afrezza	MKC-TI-126	NCT00741429	3	May-07
Afrezza	MKC-TI-117	NCT00700622	3	May-08
Afrezza	MKC-TI-139	NCT01798914	3	Oct-08
Afrezza	MKC-TI-162	NCT01196104	3	Sep-10
Afrezza	MKC-TI-164	NCT01201928	3	Oct-10
Afrezza	MKC-TI-171	NCT01445951	3	Sep-11
Afrezza	MKC-TI-175	NCT01451398	3	Nov-11
Afrezza	MKC-129	-	-	
Afrezza	MKC-143	-	-	
Afrezza	MKC-TI-025	-	-	
Afrezza	MKC-TI-027	-	-	
Afrezza	MKC-TI-104	-	-	
Afrezza	MKC-TI-110	-	-	
Afrezza	MKC-TI-111	-	-	

Brand Name	Trial Label from Med Review	NCT ID	Phase	Study Start
Afrezza	MKC-TI-123	-	-	
Afrezza	MKC-TI-140	-	-	
Afrezza	MKC-TI-141	-	-	
Afrezza	MKC-TI-142	-	-	
Afrezza	MKC-TI-159	-	-	
Afrezza	PDC-INS-0001	-	-	
Afrezza	PDC-INS-0001A	-	-	
Afrezza	PDC-INS-0001B	-	-	
Afrezza	PDC-INS-0001C	-	-	
Afrezza	PDC-INS-0002A		-	
Afrezza	PDC-INS-0003	-	-	
Afrezza	PDC-INS-0003A	-	-	
Afrezza	PDC-INS-0004	-	-	
Afrezza	PDC-INS-0004A	-	-	
Afrezza	PDC-INS-0006	-	-	
Afrezza	PDC-INS-0007	-	-	
Afrezza	PDC-INS-0011	-	-	
Afrezza			**NDA Submission**	**Mar-09**
Basaglar	ABEI	NCT01374178	1	Jun-11
Basaglar	ABEA	NCT01476345	1	Nov-11
Basaglar	ABEE	NCT01600950	1	May-12
Basaglar	ABEM	NCT01634165	1	Jul-12
Basaglar	ABEO	NCT01688635	1	Sep-12
Basaglar	ABEV	NCT02955953	1	Nov-16
Basaglar	ABEN		1	
Basaglar	**ABEB**	**NCT01421147**	**3**	**Aug-11**
Basaglar	ABEC	NCT01421459	3	Sep-11
Basaglar	ABER	NCT02302716	3	Dec-14
Basaglar			**NDA Submission**	**Oct-13**
Toujeo	PKD11627	NCT01195454	1	Aug-10
Toujeo	TDR11626	NCT01349855	1	Mar-11
Toujeo	PKD12270	NCT01493115	1	Nov-11
Toujeo	PDY12335	NCT01676233	1	Sep-12
Toujeo	PKD13560	NCT01838083	1	Apr-13
Toujeo		NCT02536859	1	Aug-15
Toujeo	**PDY12777**	**NCT01658579**	**2**	**Aug-12**
Toujeo	**EFC11628**	**NCT01499082**	**3**	**Dec-11**
Toujeo	EFC11629	NCT01499095	3	Dec-11
Toujeo	EFC12347	NCT01676220	3	Aug-12
Toujeo	EFC12449	NCT01689129	3	Sep-12
Toujeo	EFC12456	NCT01683266	3	Sep-12
Toujeo	EFC12512	NCT01689142	3	Sep-12
Toujeo	PDY14065	NCT02227212	3	Aug-14
Toujeo	EFC13799	NCT02320721	3	Jan-15
Toujeo		NCT02401243	3	Mar-15
Toujeo	EFC13470	NCT02585674	3	Dec-15
Toujeo	EFC13957	NCT02735044	3	Apr-16
Toujeo	EFC12814	NCT02855684	3	Aug-16
Toujeo			**NDA Submission**	**Apr-14**

Brand Name	Trial Label from Med Review	NCT ID	Phase	Study Start
Toujeo	PKD10086			
Tresiba	1876	NCT01868529	1	Jan-08
Tresiba	1991	NCT00961324	1	Jul-09
Tresiba	1988	NCT00966368	1	Aug-09
Tresiba	1989	NCT00976326	1	Aug-09
Tresiba	1994	NCT00964418	1	Aug-09
Tresiba	3765	NCT00964964	1	Aug-09
Tresiba	1977	NCT00992537	1	Oct-09
Tresiba	3538	NCT01002768	1	Oct-09
Tresiba	1990	NCT01006057	1	Nov-09
Tresiba	1995	NCT01030926	1	Dec-09
Tresiba	3762	NCT01043510	1	Jan-10
Tresiba	3678	NCT01076634	1	Feb-10
Tresiba	1993	NCT01114542	1	May-10
Tresiba	1987	NCT01154881	1	Jun-10
Tresiba	1992	NCT01151072	1	Jun-10
Tresiba	1996	NCT01135927	1	Jun-10
Tresiba	3857	NCT01173926	1	Jul-10
Tresiba	3769	NCT01193387	1	Aug-10
Tresiba	1999	NCT01437592	1	Sep-11
Tresiba	4000	NCT01623375	1	Jun-12
Tresiba	3999	NCT01704417	1	Oct-12
Tresiba	4227	NCT02536859	1	Aug-15
Tresiba	**1835**	**NCT00612040**	**2**	**Jan-08**
Tresiba	1836	NCT00611884	2	Jan-08
Tresiba	3569	NCT00841087	2	Jan-09
Tresiba	**3579**	**NCT00982644**	**3**	**Sep-09**
Tresiba	3582	NCT00972283	3	Sep-09
Tresiba	3583	NCT00982228	3	Sep-09
Tresiba	3668	NCT01006291	3	Nov-09
Tresiba	3580	NCT01046110	3	Jan-10
Tresiba	3585	NCT01074268	3	Feb-10
Tresiba	3586	NCT01059799	3	Feb-10
Tresiba	3724	NCT01068678	3	Feb-10
Tresiba	3672	NCT01068665	3	Mar-10
Tresiba	3718	NCT01076647	3	Mar-10
Tresiba	3770	NCT01079234	3	Mar-10
Tresiba	3839	NCT01135992	3	Jun-10
Tresiba	3846	NCT01326026	3	Mar-11
Tresiba	3923	NCT01364428	3	Jun-11
Tresiba	3948	NCT01388361	3	Sep-11
Tresiba	3561	NCT01513473	3	Jan-12
Tresiba	3874	NCT01569841	3	Apr-12
Tresiba	3943	NCT01570751	3	Apr-12
Tresiba	3944	NCT01664247	3	Oct-12
Tresiba	3587	NCT01849289	3	Jun-13

Brand Name	Trial Label from Med Review	NCT ID	Phase	Study Start
Tresiba	4060	NCT01880736	3	Jun-13
Tresiba	3995	NCT02034513	3	Jan-14
Tresiba	3998	NCT02030600	3	Jan-14
Tresiba			**NDA Submission**	**Sep-11**
Ryzodeg70/30	1718	NCT01865279	1	Dec-05
Ryzodeg70/30	1719	NCT01865292	1	Aug-06
Ryzodeg70/30	1738	NCT01865305	1	Sep-06
Ryzodeg70/30	1740	NCT01865318	1	Sep-06
Ryzodeg70/30	1788	NCT01865331	1	Dec-06
Ryzodeg70/30	1790	NCT01868555	1	Dec-07
Ryzodeg70/30	1959	NCT01868568	1	Apr-08
Ryzodeg70/30	1985	NCT01868581	1	May-08
Ryzodeg70/30	3539	NCT00993096	1	Sep-09
Ryzodeg70/30	1977	NCT00992537	1	Oct-09
Ryzodeg70/30	1983	NCT01051102	1	Jan-10
Ryzodeg70/30	1978	NCT01134224	1	May-10
Ryzodeg70/30	1980	NCT01125553	1	May-10
Ryzodeg70/30	1982	NCT01138488	1	Jun-10
Ryzodeg70/30	3857	NCT01173926	1	Jul-10
Ryzodeg70/30	1981	NCT01174303	1	Aug-10
Ryzodeg70/30	3834	NCT01455142	1	Oct-11
Ryzodeg70/30	1979	NCT01590836	1	Apr-12
Ryzodeg70/30	1984	NCT02844790	1	Jul-16
Ryzodeg70/30	**1791**	**NCT00614055**	**2**	**Jan-08**
Ryzodeg70/30	1792	NCT00613951	2	Jan-08
Ryzodeg70/30	3570	NCT00842361	2	Jan-09
Ryzodeg70/30	**3594**	**NCT00978627**	**3**	**Aug-09**
Ryzodeg70/30	3592	NCT01009580	3	Nov-09
Ryzodeg70/30	3590	NCT01045707	3	Jan-10
Ryzodeg70/30	3593	NCT01045447	3	Jan-10
Ryzodeg70/30	3597	NCT01059812	3	Feb-10
Ryzodeg70/30	3896	NCT01272193	3	Jan-11
Ryzodeg70/30	3844	NCT01365507	3	Jun-11
Ryzodeg70/30	3940	NCT01513590	3	Jan-12
Ryzodeg70/30	3941	NCT01680341	3	Aug-12
Ryzodeg70/30	3996	NCT01713530	3	Feb-13
Ryzodeg70/30	4003	NCT01814137	3	Mar-13
Ryzodeg70/30	3816	NCT01835431	3	Oct-13
Ryzodeg70/30	4243	NCT02648217	3	Jan-16
Ryzodeg70/30	3598	NCT02762578	3	May-16
Ryzodeg70/30	4266	NCT02906917	3	Sep-16
Ryzodeg70/30			**NDA Submission**	**Sep-11**

Table 9: National Drug Codes Insulin Claims

National Drug Code (NDC)	Proprietary Name	Manufacturer
00002751001	HUMALOG	Eli Lilly & Company
00002751017	HUMALOG	Eli Lilly & Company
00002751101	HUMALOG MIX 75/25	Eli Lilly & Company
00002751201	HUMALOG MIX 50/50	Eli Lilly & Company
00002751559	HUMALOG	Eli Lilly & Company
00002751601	HUMALOG	Eli Lilly & Company
00002751659	HUMALOG	Eli Lilly & Company
00002771227	HUMALOG	Eli Lilly & Company
00002811001	ILETIN PZI	Eli Lilly & Company
00002811101	ILETIN II PZI PORK	Eli Lilly & Company
00002811201	ILETIN II PZI BEEF	Eli Lilly & Company
00002814001	ILETIN PZI	Eli Lilly & Company
00002821001	ILETIN REGULAR I	Eli Lilly & Company
00002821101	ILETIN II REGULAR PORK	Eli Lilly & Company
00002821201	ILETIN II REG. BEEF	Eli Lilly & Company
00002821501	HUMULIN R	Eli Lilly & Company
00002821517	HUMULIN R	Eli Lilly & Company
00002821591	RELION HUMULIN R	Eli Lilly & Company
00002821601	HUMULIN BR	Eli Lilly & Company
00002821759	HUMULIN R	Eli Lilly & Company
00002824001	ILETIN REGULAR I	Eli Lilly & Company
00002831001	ILETIN NPH I	Eli Lilly & Company
00002831101	ILETIN II NPH PORK	Eli Lilly & Company
00002831201	ILETIN II NPH BEEF	Eli Lilly & Company
00002831501	HUMULIN N	Eli Lilly & Company
00002831517	HUMULIN N	Eli Lilly & Company
00002831591	RELION HUMULIN N	Eli Lilly & Company
00002831759	HUMULIN N	Eli Lilly & Company
00002834001	ILETIN NPH I	Eli Lilly & Company
00002841001	ILETIN LENTE I	Eli Lilly & Company
00002841101	ILETIN II LENTE PORK	Eli Lilly & Company
00002841201	ILETIN II LENTE BEEF	Eli Lilly & Company
00002841501	HUMULIN L	Eli Lilly & Company
00002844001	ILETIN LENTE I	Eli Lilly & Company
00002850001	ILETIN II REGULAR PORK	Eli Lilly & Company
00002850101	HUMULIN R CONCENTRATED U-500	Eli Lilly & Company
00002851001	ILETIN SEMILENTE	Eli Lilly & Company
00002854001	ILETIN SEMILENTE	Eli Lilly & Company
00002861001	ILETIN ULTRALENTE	Eli Lilly & Company
00002861501	HUMULIN U	Eli Lilly & Company
00002864001	ILETIN ULTRALENTE	Eli Lilly & Company
00002871501	HUMULIN 70/30	Eli Lilly & Company
00002871517	HUMULIN 70/30	Eli Lilly & Company
00002871591	RELION HUMULIN 70/30	Eli Lilly & Company
00002871759	HUMULIN 70/30	Eli Lilly & Company
00002872559	HUMALOG PEN	Eli Lilly & Company
00002873001	HUMULIN N PEN	Eli Lilly & Company
00002873059	HUMULIN N PEN	Eli Lilly & Company

National Drug Code (NDC)	Proprietary Name	Manufacturer
00002877001	HUMULIN 70/30 PEN	Eli Lilly & Company
00002877059	HUMULIN 70/30 PEN	Eli Lilly & Company
00002879359	HUMALOG MIX 50/50	Eli Lilly & Company
00002879459	HUMALOG MIX 75/25 PEN	Eli Lilly & Company
00002879701	HUMALOG MIX 75/25	Eli Lilly & Company
00002879759	HUMALOG MIX 75/25	Eli Lilly & Company
00002879801	HUMALOG MIX 50/50	Eli Lilly & Company
00002879859	HUMALOG MIX 50/50	Eli Lilly & Company
00002879901	HUMALOG	Eli Lilly & Company
00002879959	HUMALOG	Eli Lilly & Company
00002880359	HUMULIN 70/30 KWIKPEN	Eli Lilly & Company
00002880559	HUMULIN N KWIKPEN	Eli Lilly & Company
00002951501	HUMULIN 50/50	Eli Lilly & Company
00003183310	NOVOLIN R	Novo Nordisk Inc
00003183315	NOVOLIN R	Novo Nordisk Inc
00003183410	NOVOLIN N	Novo Nordisk Inc
00003183415	NOVOLIN N PENFILL	Novo Nordisk Inc
00003183510	NOVOLIN L	Novo Nordisk Inc
00003183710	NOVOLIN 70/30	Novo Nordisk Inc
00003183715	NOVOLIN 70/30 PENFILL	Novo Nordisk Inc
00003244110	INSULIN, PURIFIED SEMILENTE PORK	Novo Nordisk Inc
00003244510	INSULIN, PURIFIED ULTRALENTE BEEF	Novo Nordisk Inc
00003352115	INSULIN	Squibb-Novo Inc
00024586903	TOUJEO	Sanofi-Aventis US LLC
00024587490	AFREZZA	Sanofi-Aventis US LLC
00024588236	AFREZZA	Sanofi-Aventis US LLC
00024588463	AFREZZA	Sanofi-Aventis US LLC
00024589463	AFREZZA	Sanofi-Aventis US LLC
00069005019	EXUBERA COMBINATION PACK 12	Pfizer
00069005053	EXUBERA COMBINATION PACK 15	Pfizer
00069005085	EXUBERA KIT	Pfizer
00069070737	EXUBERA	Pfizer
00069072437	EXUBERA	Pfizer
00088221905	LANTUS SOLOSTAR	Sanofi-Aventis US LLC
00088222033	LANTUS	Sanofi-Aventis US LLC
00088222052	LANTUS	Sanofi-Aventis US LLC
00088222060	LANTUS SOLOSTAR	Sanofi-Aventis US LLC
00088250033	APIDRA	Sanofi-Aventis US LLC
00088250052	APIDRA	Sanofi-Aventis US LLC
00088250205	APIDRA SOLOSTAR	Sanofi-Aventis US LLC
00169001771	NOVOLIN 70/30	Novo Nordisk Inc
00169004471	NOVOLIN R	Novo Nordisk Inc
00169004571	NOVOLIN N	Novo Nordisk Inc
00169007011	VELOSULIN BR	Novo Nordisk Inc
00169010001	INSULIN PURIFIED	Novo Nordisk Inc
00169011101	VELOSULIN BR	Novo Nordisk Inc
00169020001	INSULIN PURIFIED	Novo Nordisk Inc
00169022201	INSULATARD HUMAN INSULIN	Novo Nordisk Inc
00169030001	INSULIN PURIFIED	Novo Nordisk Inc
00169033301	MIXTARD HUMAN INSULIN 70/30	Novo Nordisk Inc

National Drug Code (NDC)	Proprietary Name	Manufacturer
00169183302	RELION/NOVOLIN R	Novo Nordisk Inc
00169183311	NOVOLIN R	Novo Nordisk Inc
00169183317	NOVOLIN R PENFILL	Novo Nordisk Inc
00169183318	RELION/NOVOLIN R	Novo Nordisk Inc
00169183402	RELION/NOVOLIN N	Novo Nordisk Inc
00169183411	NOVOLIN N	Novo Nordisk Inc
00169183417	NOVOLIN N PENFILL	Novo Nordisk Inc
00169183418	RELION/NOVOLIN N	Novo Nordisk Inc
00169183511	NOVOLIN L	Novo Nordisk Inc
00169183702	RELION/NOVOLIN 70/30	Novo Nordisk Inc
00169183711	NOVOLIN 70/30	Novo Nordisk Inc
00169183717	NOVOLIN 70/30 PENFILL	Novo Nordisk Inc
00169183718	RELION/NOVOLIN 70/30	Novo Nordisk Inc
00169231321	NOVOLIN R INNOLET	Novo Nordisk Inc
00169231421	NOVOLIN N INNOLET	Novo Nordisk Inc
00169231721	NOVOLIN 70/30 INNOLET	Novo Nordisk Inc
00169244010	INSULIN PURIFIED REGULAR PORK	Novo Nordisk Inc
00169244210	INSULIN PURIFIED LENTE PORK	Novo Nordisk Inc
00169244710	INSULIN PURIFIED NPH PORK	Novo Nordisk Inc
00169255013	TRESIBA	Novo Nordisk Inc
00169266015	TRESIBA	Novo Nordisk Inc
00169330312	NOVOLOG	Novo Nordisk Inc
00169347318	NOVOLIN R PENFILL	Novo Nordisk Inc
00169347418	NOVOLIN N PENFILL	Novo Nordisk Inc
00169347718	NOVOLIN 70/30 PENFILL	Novo Nordisk Inc
00169351215	INSULIN STANDARD REGULAR	Novo Nordisk Inc
00169352215	INSULIN STANDARD NPH	Novo Nordisk Inc
00169352815	INSULIN STANDARD LENTE	Novo Nordisk Inc
00169355215	INSULIN STANDARD SEMILENTE	Novo Nordisk Inc
00169357215	INSULIN STANDARD ULTRALENTE	Novo Nordisk Inc
00169368213	NOVOLOG MIX 70/30	Novo Nordisk Inc
00169368512	NOVOLOG MIX 70/30	Novo Nordisk Inc
00169368712	LEVEMIR	Novo Nordisk Inc
00169369619	NOVOLOG MIX 70/30	Novo Nordisk Inc
00169633910	NOVOLOG FLEXPEN	Novo Nordisk Inc
00169643810	LEVEMIR FLEXTOUCH	Novo Nordisk Inc
00169643910	LEVEMIR	Novo Nordisk Inc
00169750111	NOVOLOG	Novo Nordisk Inc
00403296118	HUMULIN N	Compumed Pharmaceuticals Inc
00403344918	HUMULIN R	Compumed Pharmaceuticals Inc
23490668700	INSULIN HUMAN REGULAR	Palmetto State Pharmaceuticals
35356010200	HUMALOG	Quality Care Products LLC
49999099310	HUMULIN	Quality Care Products LLC
49999099410	LANTUS	Quality Care Products LLC
54569165101	ILETIN NPH I	A-S Medication Solutions LLC
54569165102	ILETIN NPH I	A-S Medication Solutions LLC
54569165200	ILETIN II REG. PORK	A-S Medication Solutions LLC
54569165202	ILETIN II REG. PORK	A-S Medication Solutions LLC
54569231800	HUMULIN N	A-S Medication Solutions LLC
54569231801	HUMULIN N	A-S Medication Solutions LLC

National Drug Code (NDC)	Proprietary Name	Manufacturer
54569231900	HUMULIN R	A-S Medication Solutions LLC
54569231901	HUMULIN R	A-S Medication Solutions LLC
54569255700	HUMULIN L	A-S Medication Solutions LLC
54569255701	HUMULIN L	A-S Medication Solutions LLC
54569281600	INSULIN PURIFIED LENTE PORK	A-S Medication Solutions LLC
54569281700	INSULIN PURIFIED REGULAR PORK	A-S Medication Solutions LLC
54569289100	ILETIN PORK NPH	A-S Medication Solutions LLC
54569289101	ILETIN PORK NPH	A-S Medication Solutions LLC
54569291800	NOVOLIN 70/30	A-S Medication Solutions LLC
54569291801	NOVOLIN 70/30	A-S Medication Solutions LLC
54569291802	NOVOLIN 70/30	A-S Medication Solutions LLC
54569295100	ILETIN REGULAR I	A-S Medication Solutions LLC
54569295101	ILETIN REGULAR I	A-S Medication Solutions LLC
54569346700	HUMULIN 70/30	A-S Medication Solutions LLC
54569346701	HUMULIN 70/30	A-S Medication Solutions LLC
54569383300	NOVOLIN R	A-S Medication Solutions LLC
54569383301	NOVOLIN R	A-S Medication Solutions LLC
54569383302	NOVOLIN R	A-S Medication Solutions LLC
54569383400	NOVOLIN L	A-S Medication Solutions LLC
54569383401	NOVOLIN L	A-S Medication Solutions LLC
54569383500	NOVOLIN N	A-S Medication Solutions LLC
54569383501	NOVOLIN N	A-S Medication Solutions LLC
54569383502	NOVOLIN N	A-S Medication Solutions LLC
54569532100	HUMALOG MIX 75/25	A-S Medication Solutions LLC
54569560500	LANTUS	A-S Medication Solutions LLC
54569630000	LEVEMIR	A-S Medication Solutions LLC
54569630100	LEVEMIR	A-S Medication Solutions LLC
54569630101	LEVEMIR	A-S Medication Solutions LLC
54569643500	HUMALOG	A-S Medication Solutions LLC
54569646200	LANTUS SOLOSTAR	A-S Medication Solutions LLC
54569646201	LANTUS SOLOSTAR	A-S Medication Solutions LLC
54569657000	LEVEMIR FLEXTOUCH	A-S Medication Solutions LLC
54569658400	NOVOLOG	A-S Medication Solutions LLC
54569658500	HUMALOG	A-S Medication Solutions LLC
54569658600	NOVOLOG	A-S Medication Solutions LLC
54569658700	NOVOLOG FLEXPEN	A-S Medication Solutions LLC
54868011200	LEVEMIR	Physicians Total Care
54868142801	ILETIN NPH I	Physicians Total Care
54868142901	HUMULIN N	Physicians Total Care
54868208901	ILETIN REGULAR I	Physicians Total Care
54868238001	NOVOLIN N	Physicians Total Care
54868274600	HUMULIN 70/30	Physicians Total Care
54868277700	NOVOLOG	Physicians Total Care
54868347400	NOVOLIN 70/30	Physicians Total Care
54868359800	NOVOLIN R	Physicians Total Care
54868361900	HUMULIN R	Physicians Total Care
54868438100	HUMALOG MIX 75/25	Physicians Total Care
54868462600	LANTUS	Physicians Total Care
54868510800	HUMALOG	Physicians Total Care
54868520100	NOVOLOG MIX 70/30	Physicians Total Care

National Drug Code (NDC)	Proprietary Name	Manufacturer
54868532700	NOVOLOG MIX 70/30	Physicians Total Care
54868532701	NOVOLOG MIX 70/30	Physicians Total Care
54868576500	LANTUS	Physicians Total Care
54868582400	HUMULIN 50/50	Physicians Total Care
54868583600	HUMALOG	Physicians Total Care
54868588300	LEVEMIR	Physicians Total Care
54868589900	HUMALOG PEN	Physicians Total Care
54868605400	NOVOLOG FLEXPEN	Physicians Total Care
54868623100	LANTUS SOLOSTAR	Physicians Total Care
55045350601	HUMULIN R	Dispensing Solutions Inc
55045350801	NOVOLIN 70/30	Dispensing Solutions Inc
55045360201	HUMALOG	Dispensing Solutions Inc
55045362401	HUMULIN 70/30	Dispensing Solutions Inc
55045368501	LANTUS	Dispensing Solutions Inc
58016478801	HUMULIN N	Southwood Pharm Inc
59060183302	NOVOLIN R	Novo Nordisk Inc
59060183402	NOVOLIN N	Novo Nordisk Inc
59060183702	NOVOLIN 70/30	Novo Nordisk Inc
59060231404	RELION NOVOLIN N INNOLET	Novo Nordisk Inc
59060231704	RELION NOVOLIN 70/30 INNOLET	Novo Nordisk Inc
66143751005	LISPRO-PFC	Midwest IV
68115070905	NOVOLIN R PENFILL	Dispensexpress Inc
68115072810	HUMULIN R	Dispensexpress Inc
68115072905	HUMULIN N PEN	Dispensexpress Inc
68115074610	HUMALOG	Dispensexpress Inc
68115083910	LANTUS	Dispensexpress Inc
68258598301	HUMALOG MIX 75/25	Dispensing Solutions Inc
68258889903	NOVOLOG FLEXPEN	Dispensing Solutions Inc
68258892703	LEVEMIR	Dispensing Solutions Inc
68258892803	NOVOLOG	Dispensing Solutions Inc
68258893001	NOVOLOG MIX 70/30	Dispensing Solutions Inc
68258893103	LANTUS SOLOSTAR	Dispensing Solutions Inc
68258896701	NOVOLOG	Dispensing Solutions Inc
68258897701	LEVEMIR	Dispensing Solutions Inc
68258898501	HUMULIN N	Dispensing Solutions Inc
68258898601	NOVOLIN N	Dispensing Solutions Inc

Table 10: Insulin Combinations

Combinations	Prescription Claims	Percentage of Claims
Bolus Only	2,672,920	9.24
Basal Only	5,851,299	20.23
Both	17,878,294	61.81
Other	2,521,207	8.72
Total	28,923,720	100

Figure 7: Average Residuals over Time

Table 11: Price Effects using Pre- and Post-ACA Time Trends

	(1) Original Time Trends	(2) ACA Time Trends
Phase 3 Shocks		
1^{st} Pipeline Shock$_t$	-0.726	2.405***
	(0.795)	(0.473)
2^{nd} Pipeline Shock$_t$	-1.147	-3.304***
	(0.912)	(1.081)
3^{rd} Pipeline Shock$_t$	2.285**	1.527
	(1.053)	(0.952)
4^{th} Pipeline Shock$_t$	2.263**	3.433***
	(1.142)	(1.041)
Time	0.715***	
	(0.0957)	
Time^2	0.0323***	
	(0.00636)	
pre_aca		0.214***
		(0.0502)
post_aca		1.879***
		(0.130)
Quarter 2	-0.643	-0.896*
	(0.455)	(0.468)
Quarter 3	-0.278	0.0643
	(0.492)	(0.493)
Quarter 4	-0.412	0.0656
	(0.516)	(0.491)
Health Plan Type		
Exclusive Provider Organization	-3.436***	-3.362***
	(0.308)	(0.311)
Health Maintenance Organization	-6.775***	-6.822***
	(0.307)	(0.307)
Non-capitated Point of Service (POS)	-3.508***	-3.542***
	(0.301)	(0.299)
Preferred Provider Organization	-4.923***	-4.964***
	(0.238)	(0.238)
Capitated or Partially-capitated POS	-9.680***	-9.704***
	(0.553)	(0.553)
Consumer Driven Health Plan	-7.624***	-7.621***
	(0.306)	(0.307)
High Deductible Health Plan	-7.007***	-7.024***
	(0.319)	(0.319)
Constant	22.80***	19.45***
	(0.758)	(0.636)
R-squared	0.222	0.222
Observations	27,359,428	27,359,428
Number of drugs	122	122

Note. All estimates are obtained using OLS with drug-level fixed effects. The dependent variable is inflation-adjusted price per mL in both specifications. Standard errors are clustered at the drug-quarter level.
* Statistically significant at the 10 percent level
** Statistically significant at the 5 percent level
*** Statistically significant at the 1 percent level