Eating the Seed Corn? The Impact of Generic Drug Entry on Innovation in Animal Health

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Abstract

Firms may respond to increased competition by changing the kind of research they conduct, as well as the amount. After motivating our paper with a model of a firm choosing between original and incremental R&D, we use the US animal pharmaceutical sector as a test case. We examine the impact of generic competition on annual drug approvals, following the passage of legislation in 1989 that created a regulatory path for generic drug approval. In an extension, we use the expiry of patents applied for prior to legislation as an instrument to control for the endogeneity of generic competition in different drug categories. We show drugmakers strongly responded to generic competition in their drug category by reducing original R&D (drugs with a novel active ingredient) and increasing incremental R&D, with no net change in total drug approvals per year.

*The views expressed are those of the authors and should not be attributed to the Economic Research Service or USDA.

A large literature has examined whether firms increase or decrease research and development (R&D) activities in response to competition (Cohen 2010). But R&D is not a homogenous activity. Firms respond to changing market conditions by changing the kind of research they do as well as the amount. This paper is largely concerned with how firms shift between developing new product lines (which we call "original" R&D) and improving existing ones (which we call "incremental" R&D) in the presence of changing competitive conditions.

Our case study is the US animal pharmaceutical industry. This sector is an ideal study subject for the economics of innovation. Like the human pharmaceutical sector, it is research intensive and its research outputs (drugs) leave behind extensive documentation. Unlike the human pharmaceutical sector, there are no significant intermediaries between consumers and drug manufacturers. This means consumers are likely to be sensitive to the prices of drugs, which magnifies the impact of changes to the competitive landscape relative to human health. Importantly for our purposes, there is also a mix of original and incremental R&D, and it is straightforward to differentiate the two.

We examine the impact of a shock to the competitive landscape in 1989. In that year, legislation created a regulatory path for generic versions of off-patent animal drugs. Generic entrants subsequently proliferated, but in a heterogeneous fashion across categories of drugs. We show annual drug approvals were barely perturbed by the onset of generic competition in the same category. Yet this apparent placidity masked significant shifts in the kinds of research undertaken. In drug categories facing more generic competition, drugmakers shifted R&D resources away from original R&D and towards incremental R&D. These results are economically significant. Our baseline estimate is that a move from no generic competition to the median is associated with a 61% decline in the annual flow of original drug approvals. This is offset by an increase in incremental drug approvals, so that total drug approvals are unchanged. In an extension, we use the expiry of patents with applications filed before generic drug legislation as an instrument to control for the endogeneity of generic competition. This exercise tends to strengthen our results.

We also develop a model to explain why firms would shift resources from original to incremental R&D in the presence of competition. Our model is closely related to one presented in Charnov (1976), a classic paper in ecology about optimal foraging behavior: we show our

optimality condition converge to his as the discount rate falls to zero. In our model, a firm allocates incremental R&D time to a particular product line, or conducts original R&D to develop a new product line. The latter is more costly, but the marginal value of incremental R&D is declining. We show time spent on incremental R&D per product line increases if the profitability of R&D declines or if the costs of original R&D rises. We interpret the onset of generic competition as potentially having both these effects. The presence of a generic competition may reduce the profits of future drugs in the same category, and the threat of generic copying may force firms to spend more on intellectual property rights protections.

Our results are related to three distinct literatures. First, our work is part of the large literature on the economics of innovation in the presence of competition. Cohen (2010) provides a nice overview of this literature, which tends to emphasize the ambiguity of the relationship between total R&D and competition. Bloom, Draca, and Van Reenen (2016) and Autor et al. (2017) are two recent papers examining the impact of Chinese competition on innovation in Europe and the USA respectively. They obtain opposing results (competition spurs innovation in Europe but retards it in the USA). In our case, we find no change in the number of drug approvals (original plus incremental) in response to generic competition.

Both papers focus on the impact of competition on aggregate R&D (mainly measured by patents), but each has a small section on the quality of patents (as measured by the number of subsequent citations received). Since citations are frequently used as a proxy for value, this can be interpreted as a test of how competition affects the kind of research firms do (high value or low value). Neither paper finds evidence of a shift in citations received by patents. In contrast, since our paper is focused on a particular industry, we can use a much more specific measure of original versus incremental R&D: the presence or absence of novel active ingredients. We provide evidence that this approach accurately captures original and incremental R&D. Interestingly we find patents associated with original research do not receive more citations, and is therefore consistent with this aspect of Bloom, Draca, and Van Reenen (2016) and Autor et al. (2017).

Second, because the animal pharmaceutical sector strongly resembles the human pharmaceutical sector, our results also inform the economics of innovation in healthcare (see xxx for a summary). Our results most closely complement the findings of Branstetter, Chatterjee, and

Higgins (2014), which looks at the impact of generic drug entry on early stage research in human medicine. They also find generic competition is associated with less early stage research. Nonetheless, our work differs from theirs in several ways. First, we develop a theoretical model where R&D is shifted from original to incremental R&D. Second, we take time to validate the assumptions of our model in our data. Third, we use control functions and the expiration of patents applied for prior to generic drug legislation as an instrument to control for the endogeneity of generic drug competition.

As in Branstetter, Chatterjee, and Higgins (2014), our results illustrate the inherent trade-off between ex-ante and ex-post welfare in the design of intellectual property rights. The finite life of patents is premised on the desire to provide some incentive to innovators to develop new drugs (increasing ex-ante welfare), but also to ensure these innovations are eventually produced in a competitive market (maximizing ex-post welfare). While the availability of generic drugs certainly increases access to pharmaceutical innovations, our results indicate there is a strong off-setting impact on the incentive to develop original drugs. Note, however, that attempting to compute the welfare effects of the generic drug policy is beyond the scope of this paper.

Finally, our work informs the growing interest among policy-makers in the incentives for drug development in the animal health industry (PACCARB 2017). Policy interest in this realm has grown in tandem with concerns about antibiotic resistance. Any use of antibiotics can raise the risk of bacteria becoming resistant, and animal agriculture uses a large share of all antibiotics. Because many of the same bacteria infect humans as well as animals, and because unrelated bacteria may also exchange genes for resistance with each other, the development of antibiotic resistant strains of bacteria in animals also poses a threat to human health. Reducing the use of antibiotics in animal health can occur through two channels: regulating drugs that exist, and developing incentives for the discovery of new drugs that may substitute for antibiotics. The latter requires understanding how the animal pharmaceutical sector responds to incentives, such as the presence or absence of generic competition.

Our paper is organized as follows. Section 1 lays out our motivating theoretical model. Because it is not commonly studied in the economics of innovation, section 2 provides a brief overview of the animal health industry. Section 3 describes our dataset and constructed variables. In this section, we also use the data to validate several of the assumptions underlying our model. We

provide evidence, for example, that our definition of "original" research in our data matches our theoretical assumptions, and that incremental research in our data has declining marginal value. Section 4 presents our baseline results, establishing a strong negative correlation between the annual number of original drug approvals and the extent of generic competition, but no correlation between the extent of generic competition and all (original and incremental) drug approvals. Section 5 turns to the question of endogeneity, and attempts to demonstrate the correlations of section 4 are causal. We use three approaches: two deploy additional controls, and a third uses instrumental variables and control functions. Finally, in section 6 we offer some brief discussion of our results and suggestions for future research.

1. Motivating Model

Consider a researcher working to develop new products and improve existing products in a narrowly defined product category. This researcher can allocate her time in one of two ways: incremental R&D or original R&D. Time is continuous and she discounts the future at rate δ.

Incremental R&D develops new products or improved versions of existing products, but stays within an existing main inventive concept. For example, in our empirical sections, we define a product line by the active ingredient in a drug. Incremental R&D on this active ingredient could take many forms. It could consist of developing a new version of the drug that can be taken orally instead of via injection. It could consist of doing clinical studies to add a new claim to the drug (for example, that it can be used to treat a second disease). It could consist of developing a new version of the drug that can be used in a new species.

Original R&D develops a new inventive concept that spawns an entire new product line. For example, in our empirical sections, we define original invention to be drugs with novel active ingredients. These original inventions then serve as the platform upon which incremental R&D is conducted.

For this motivating example, we abstract away from many topics of interest such as demand for products, substitutability among product lines, market structure, and the stochastic nature of R&D. We simplify to focus on the trade-off between original and incremental R&D. We assume the value of allocating time t to a given product line is $\pi(t,\varepsilon)$, where ε is an exogenous (to the researcher) variable that determines the profitability of R&D. The function $\pi(t,\varepsilon)$ can be

interpreted in a number of ways. If incremental R&D consists of developing a series of product variations (such as new drugs), it can be interpreted as the present-discounted value of sequentially selling the intellectual property rights on each product to a manufacturer, until product development ceases at time t. Alternatively, we can suppose incremental R&D consists of finetuning and perfecting a single product over time t. In this case $\pi(t,\varepsilon)$ can be interpreted as the present-discounted value of selling the patent rights to the version of the product that exists after time t spent on incremental R&D.

We assume $\pi_1 > 0$, $\pi_{11} < 0$, and that $\lim_{t\to\infty} \pi(t,\varepsilon) = c(\varepsilon) < \infty$. This asserts that the value of a product line is increasing in the time spent on incremental R&D, but that the marginal value of incremental R&D declines over time and eventually falls towards 0. Product lines have a finite value; no amount of incremental R&D can push the value of a product line above some level $c(\varepsilon)$. We further assume that $\pi_2 > 0$ and $\pi_{12} \leq 0$. This asserts that ε is defined so that a positive shock increases profitability of R&D, and that the impact of a positive shock does not increase in the time spent on incremental R&D at a rate faster than the discount rate.

We assume starting a new product line has a sunk cost I, but implicitly assume the cost of time spent on incremental R&D is 0. This assumption is not crucial, and we could incorporate non-zero incremental R&D costs and re-define $\pi(t,\varepsilon)$ to be R&D value net of labor costs (if we did this, it would have a maximum at some finite t and then decline, rather than asymptote towards $c(\varepsilon)$).

The problem of a researcher is to decide how much time to allocate to incremental R&D on each product line before starting a new one with original R&D. Let $V(t,\varepsilon)$ denote the present-discounted value of the fixed strategy that allocates t to each product line before developing a new one:

$$V(t,\varepsilon) = \pi(t,\varepsilon) + e^{-\delta t}\left(V(t,\varepsilon) - I\right) \tag{0.1}$$

We can divide $V(t,\varepsilon)$ into two components. First, if the researcher devotes t to incremental R&D on the current product line, she obtains $\pi(t,\varepsilon)$ from it. After this time has elapsed, she creates a new product line at cost I and finds herself back in the same position, ready to earn $V(t,\varepsilon)$. This second component, worth $V(t,\varepsilon) - I$, is discounted by $exp(-\delta t)$. Solving for $V(t,\varepsilon)$:

$$V(t,\varepsilon) = \frac{\pi(t,\varepsilon) - e^{-\delta t} I}{1 - e^{-\delta t}} \tag{0.2}$$

The problem of a researcher is to find t^* that maximizes equation (0.2). The first order condition to this equation is:

$$V_1 = \frac{\left(1 - e^{-\delta t}\right)\pi_1 - \delta e^{-\delta t}\pi + \delta e^{-\delta t} I}{\left(1 - e^{-\delta t}\right)^2} \tag{0.3}$$

Setting this equal to zero, we arrive at the optimality condition:

$$\pi_1 = \frac{e^{-\delta t}\left(\pi - I\right)}{\left(1 - e^{-\delta t}\right)/\delta} \tag{0.4}$$

This result is an analogue of Charnov (1976)'s seminal result about exploration vs. exploitation in optimal foraging behavior. Charnov's work is in the context of ecology and he models the problem of an animal that must choose between continuing to forage in a fixed location or to seek out a new location to forage. Just as in our model, the marginal returns to time spent foraging in any given location fall to zero in the long run, but a fixed cost must be endured to seek out a new location. Charnov assumes animals want to maximize the *average* return on foraging and shows the optimal time spent in any location equates the marginal value from staying in the location to the average returns to a location (inclusive of fixed costs).

Unlike animals, we assume our researcher discounts the future. However, as the discount rate goes to zero the right-hand side of equation (0.4) converge to Charnov's result (as we apply l'hopital's rule):

$$\lim_{\delta \to 0} \frac{\delta e^{-\delta t}\left(\pi - I\right)}{1 - e^{-\delta t}} = \lim_{\delta \to 0} \frac{\left(e^{-\delta t} - \delta t e^{-\delta t}\right)\left(\pi - I\right)}{t e^{-\delta t}} = \frac{\pi - I}{t} \tag{0.5}$$

Essentially, we show a researcher should allocate time to incremental research until the marginal return of such research equates to the discounted "average" rate of return on a new product line (where we use a weighted average that gives less and less weight to later time).

All that remains is to establish the second-order sufficient condition:

$$V_{11} = \frac{\pi_{11}}{1 - e^{-\delta t}} - \frac{\delta e^{-\delta t}\left(\pi - I\right)}{1 - e^{-\delta t}} \frac{\delta}{1 - e^{-\delta t}} - \frac{2\delta e^{-\delta t}}{1 - e^{-\delta t}} V_1 \tag{0.6}$$

Imposing the first order condition and substituting in equation (0.4) this can be rewritten as:

$$V_{11} = \frac{\pi_{11} - \delta\pi_1}{1 - e^{-\delta t}} < 0 \tag{0.7}$$

which establishes the condition.

Next, we turn to the question that animates our paper. What is the impact of a negative shock to the profits of a product line on the share of time spent on incremental vs. original R&D?

Rewrite the FOC as:

$$G(t, \varepsilon, I) = \left(1 - e^{-\delta t}\right)\pi_1 - \delta e^{-\delta t}(\pi - I) \tag{0.8}$$

Where $G(t^*, \varepsilon, I) = 0$. Having established $V_{11} < 0$ at t^*, by the implicit function theorem, the sign of $\partial t^* / \partial \varepsilon$ is equal to the sign of $\partial G / \partial \varepsilon$:

$$\frac{\partial G}{\partial \varepsilon} = \left(1 - e^{-\delta t}\right)\pi_{12} - \delta e^{-\delta t}\pi_2 \tag{0.9}$$

Given our assumption that $\pi_{12} \leq 0$ and $\pi_2 > 0$, equation (0.9) is negative, and thus $\partial t^* / \partial \varepsilon < 0$.

Thus, a negative shock to the profitability of product lines will increase the time t^* spent on incremental R&D and decrease the number of original product lines per unit of time.

Finally, we consider an alternative framing. What if the cost I of original R&D rises? This could describe a situation where a previously uncontested research space faces the risk of competition from a new entrant. To secure the same profit stream $\pi(t, \varepsilon)$, the inventor must now invest additional resources, such as securing a patent. As before, the sign of $\partial t^* / \partial I$ is equal to the sign of $\partial G / \partial I$:

$$\frac{\partial G}{\partial I} = \delta e^{-\delta t} \tag{0.10}$$

This is clearly positive, and so an increase in the cost of original R&D will also increase the time t^* spent on incremental R&D and decrease the number of original product lines per unit of time.

To summarize, when the returns to incremental R&D decline over time, but original R&D involves extra cost, we have shown that a decline in profitability leads firms to conduct original R&D less often. In this model, we have simply assumed the researcher has no outside option. We feel this a

realistic model of the short-term. Researchers spend a long time building sector-specific human capital that allows them to conduct R&D in a particular research domain. A decline in the profitability of R&D in this field may deter new entrants from investing in the same human capital, but for researchers already in the field, these investments are sunk costs. Exit may not be optimal if the returns to R&D remain higher than an outside option that requires new investment in human capital. However, in the long run as researchers retire or new opportunities arise stochastically, the total number of researchers in a field will fall as fewer enter to restock the supply of researchers.

2. An introduction to the animal health industry

The focus of our empirical exercise is the (non-human) animal pharmaceutical sector. Because this is not a sector commonly studied in the economics of innovation, in this section we briefly describe its contours, directing interested readers towards Sneeringer, Bowman, and Clancy (2018) for a more complete discussion.

To a first approximation, the animal pharmaceutical sector resembles a vastly smaller version of the human pharmaceutical sector. Animal health had 16% as many US drug approvals over 1991-2010 as human health, and 2% of human health's global annual revenues in recent years (Sneeringer, Clancy, and Bowman, unpublished). Both industries are R&D intensive. The ratio of R&D to sales was 7.8% in animal pharma in 2007 (Fuglie et al. 2011, pg. 86) and 12.7% in human pharma (National Science Board 2010, Appendix Table 4-14). Both industries' R&D relies on similar techniques to develop similar drugs to treat related (but not identical) illnesses. Costly and lengthy regulatory approval is necessary in each industry before products can be marketed, and patents play an important role in protecting products. Drugs are available either over the counter, or after receipt of a written directive from a licensed professional (prescriptions from doctors in human pharma, prescriptions or veterinary feed directives from veterinarians in animal pharma). Indeed, so similar are the businesses that six of the top seven largest companies selling animal drugs are divisions of human pharma companies (Sneeringer, Clancy, and Bowman unpublished). The exception is Zoetis, which was itself a division of the human pharma company Pfizer until it was spun off as a stand-alone company in 2013. Together, these seven companies accounted for 73% of sales in the animal health market in 2014.

Drug development in animal health follows a similar pathway as in human health. First new chemical compounds are identified and screened for useful effects. At this stage, the relevant

biological and chemical knowledge in the animal health industry has substantial overlap with the knowledge base used in human medicine. Next, after a promising compound has been identified and studied, drug makers begin to seek market approval for their drugs from the relevant regulatory authority. Passing through the regulatory pathways is separate but similar for human and veterinary drugs. In the USA, drugs for animals must seek approval from the FDA, just as human drugs must. Since the Kefauver-Hams Drug Amendments of 1962, an animal drug sponsor will need data to prove the drug is effective, that it can be manufactured according to best practices, and that it is safe. In the case of the animal pharmaceutical sector, drugs must be safe not only for the target user, but also for consumers of the food product as well as safe for the environment.

Once in the marketplace, however, the human and animal pharmaceutical sectors diverge significantly. In general, the animal health sector operates with fewer intermediaries. Third party insurance is essentially non-existent through our observation period and farmers/pet owners typically pay the market price for veterinary treatment. Neither is there any government program analogous to Medicare or Medicaid in animal health. The types of product demanded also differ. In animal agriculture, animals have a market value and farmers will not pay for treatments that exceed this value. Demand for expensive, bespoke, personalized medicine is negligible in animal agriculture. That said, willingness to pay for treatment of companion animals (i.e., pets) has grown rapidly (Einav, Finkelstein, and Gupta 2016).

The sector is a useful venue to study original versus incremental innovation because the two forms of innovation are easily identifiable. In animal health, we can directly observe the development of new products, because every new product must seek approval from the FDA. Our dataset consists of all such approved products. We define original research to be the development of drugs with a novel active ingredient, and incremental R&D to be all other (non-generic) drugs. In the next section, we provide some evidence this is a reasonable definition of original R&D.

Our empirical exercise is motivated by differential shocks to the profitability of different categories of animal health product. The 1988 Generic Animal Drug and Patent Term Restoration Act established a new category of drug approval in animal health called an abbreviated new animal drug application (ANADA). For drugs that were off patent and not subject to any other forms of market exclusivity, a generic drug manufacturer could seek FDA approval to market a previously approved drug by demonstrating their generic version is bioequivalent to the previously approved

version. Previously, a generic manufacturer would need to seek regulatory approval from the FDA using the same procedure as a new drug (i.e., demonstrating the drug's safety and efficacy via clinical trials).

The act dramatically lowered the cost of entry for generic competitors and after a few years, generic drugs began to pour onto the market, accounting for half of all drug approvals over 1992-2015. Entry was highly heterogeneous across product categories, however. By 1995, 32 out of 42 drug categories still had no generic competition, but among prescription antibiotics for horses nearly 25% of approved drugs were generics. Twenty years later, only 7 drug categories still had no generic options, but fully 80% of the prescription antibiotics available for turkeys were generics.

We interpret this shock as being exogenous to the researchers in each firm focusing on that product niche. We interpret a higher share of generic drugs in a drug category as proxying for a higher probability that any given new product development would face a (possibly imperfect) substitute marketed at competitive prices. This has the tendency either to erode the expected value of new R&D in the field or to require additional investment in patent protection to maintain profit levels. We then show this is correlated with a decrease in the number of original drug approvals, but not all drugs.

3. Data

3.1 Data Sources

Our data is primarily drawn from FDA records. The "Animal Drugs @ FDA" (https://animaldrugsatfda.fda.gov) website is a repository of information about every drug approved by the FDA. We webscraped this archive in August 2016 to generate our dataset of 2,165 approved drugs. We exploit six main pieces of information: the species the drug has been approved for, the dispensing status, the type of drug application, the class of drug (antibiotic, parasiticide or other), the originality of the drug, and the year the drug was approved.

Animal drugs are approved for 42 different species categories, including major species like cattle and cats, but also for relatively minor species, such as bees, reindeer and bears. We restrict our attention to the 7 major animal species as defined by the FDA: cats, cattle, chickens, dogs, horses, swine, and turkeys. A drug is categorized as a drug for one of these species if it has been

approved for them. In 26% of the drugs in our dataset, a drug is approved for multiple species, and these drugs are assigned to every species for which they are approved.

Turning to the dispensing status, drugs can take on a combination of four designations: unassigned, over-the-counter (OTC), prescription (RX), or veterinary feed directive (VFD). We mark a drug as OTC if its designation includes OTC, and RX if the designation status includes RX. There are 16 drugs with both an RX and OTC designation, and we assign each of these to both category. Note that VFD stands for veterinary feed directive, a designation analogous to a prescription drug for drugs delivered in animal feed introduced in the 1996 Animal Drug Availability Act. Only 5 drugs have been assigned this designation. We omit from analysis VFD drugs and those that are not assigned a dispensing status.

Our data also classifies drugs as New Animal Drug Applications (NADAs) or Abbreviated New Animal Drug Applications (ANADAs). The latter correspond to generic drugs, which are approved through an abbreviated review. Because only NADAs involve original R&D, we use them as our dependent variables. We use generic drugs, however, to compute our generic penetration measures. We discuss the construction of generic share measures in section 3.2.

Determining the antibiotic and parasiticide status of a drug involved considerably more work. The Animal Drugs @ FDA website does not identify drugs the broad therapeutic class the drug is used for (although this can be inferred from label instructions by veterinarians). It does, however, provide a complete list of the drug's active ingredients. To determine if a drug is an antibiotic, we rely on three lists of antibiotic compounds from WHO (2017), OIE (updated), FDA (2003), and FDA (2017). We consider an ingredient to be a match to any of these lists if it is an exact word match, a phonetic word match (as implemented by STATA's phonetic match), or in the case of multiple word ingredients, if the first word is an exact match. Any drug with an active ingredient matched to one of these lists is considered an antibiotic. Any drug with no active ingredients matched to these lists is considered not an antibiotic. See the appendix for more details on our assignment of drugs to different therapeutic categories.

Next, we perform exact character value matching of the listed drug ingredients, comparing them to a list of parasiticide ingredients. This list was garnered from the Merck Veterinary Manual (Stitch, undated; Dryden, undated), the website parasitipedia.net (a reference site for animal

parasites), and the veterinary professionals website dvm360. We also find phonetic matches, then manually check the matches and non-matched ingredients.

We next define drugs to be "original" if they include an active ingredient not listed among the active ingredients in drugs approved in earlier years. Drugs that are not original include novel combinations of existing active ingredients, as well as application of existing ingredients to new species and diseases. All these applications require R&D, but they are inherently more incremental than the development of novel chemical ingredients. In section 3.3, we provide evidence that originals are more frequently patented, and argue this is a reasonable validation of our assumption.

Determining the year a drug was approved involved additional work. The Animal Drugs @ FDA website does not include the approval dates or the dates drugs are withdrawn (if they are currently inactive). To determine the date drugs were approved, we obtained archived pdf versions of the FDA's annual green book, a list of all currently active animal drug approvals published annually since 1989. Fortunately, the 1989 green book lists the date at which all active drugs (as of 1989) were approved. Moreover, the 2016 green book lists the date all drugs withdrawn (as of 2016) were withdrawn. We text scrape this information to obtain approval dates for a large share of our data and withdrawal dates for all our data.

For drugs approved after 1989, we use the first year a drug appears in a green book as our proxy for the drug's approval year. Because green books are published in January, we actually assign the year preceding the green book year as the drug's approval year; for example, a NADA that first appears in the 2000 green book (published in January 2000), is assumed to have been approved in 1999. We restrict our attention to drugs approved after 1962, which is when drugs were first required to demonstrate they were effective under the Kefauver-Hams Drug Amendments.

3.2. Constructing Variables

We use the above data to construct our dependent and explanatory variables. Once drugs have been designated as original or not and assigned an approval year, species, dispensing status, and therapeutic status (antibiotic, parasiticide or other), we can count the number of drugs (either

incremental or original) in a given "species/therapeutic class/dispensing status" category that are approved in each year.

We use the active (i.e., not withdrawn) drug applications in a given category to compute the generic share. Drugs are considered active once they have been approved, through the end of our data sample (2015) or the withdrawal date, if applicable. We take the number of active generic drugs in category *c* and year *t* divided by the number of active (generic and non-generic) drugs in category *c* and year *t*. Because non-generic drugs that are approved in year *t* count towards year *t*'s generic share's denominator, in our regressions, we lag the generic share by one year to avoid simultaneity issues.

After all the preceding restrictions, our dataset is based on 1,232 approved drugs split into 42 distinct categories.

3.3 Validating our model assumptions

Our model makes three major assumptions: (1) original research is more costly than incremental research; (2) original research generates a new inventive concept or platform upon which incremental R&D is conducted; (3) the marginal value of incremental R&D declines. In our empirical exercise, we equate original R&D with drug approvals with a novel active ingredient and incremental R&D with all other drug approvals. In this section we discuss the match between our motivating theory and the data.

Is original R&D more expensive than incremental R&D in animal health?

There is little information about the cost of R&D in animal health. However, in 2011 and 2015, the industry group Health for Animals (formerly IFAH) conducted surveys of member firms that included questions about the cost of new product development and the costs of adding an indication to existing drugs. In 2011, surveyed US firms reported the average cost of developing a new pharmaceutical product with a new active ingredient was $38.8mn for a food animal and $21.6mn for a companion animal. They reported the cost of adding a new species was $11.3mn for food animals and $6.7mn for companion animals (BioBridge 2012). The 2015 survey did not disclose costs of new product development, but 70% of respondents reported there had been an increase in the cost of new product development, suggesting costs were at least as high as in 2011. In the same survey, US firms reported the costs of adding a new claim or use to an existing

pharmaceurical product was $6.3mn for food animals and $4mn for companion animals (BioBridge 2015).

Does original R&D generate a platform upon which incremental R&D builds in animal health?

By definition, drugs that we characterize as "original R&D" will precede their incremental successors (as is necessary in our model). This is because the first drug to contain a given active ingredient is denoted as "original" and all subsequent drugs with that ingredient (and no novel additions) are denoted as incremental. As a form of cross-validation, we assess the probability a given drug approval has an associated patent.

This test can potentially disprove our assumptions. At least in principle, a patent is only granted for inventions that are novel and non-obvious (as well as useful), at the time of application. If incremental drugs receive more patents than original drugs, this could indicate our definition of original R&D in animal health is wrong. It would imply the drugs we label as "incremental" are novel and non-obvious (in the judgment of patent examiners), even taking into account the existence of the supposedly "original" drug.

To test this, we scraped associated patent data from the Animal Drugs @ FDA website and our archived Green Books. This information has been provided to the public since the passage of the 1988 Generic Animal Drug and Patent Term Restoration Act. In Table 1 we run regressions to assess the probability a drug has ever been protected by patents, as a function of whether or not it is designated original.

Table 1. Probability of Being Patented if Original

	Dependent variable: y_i = 1 if drug *i* has associated patents			
	(1)	(2)	(3)	(4)
Intercept	0.25***	-1.10***		
	(0.015)	(0.076)		
Original	0.22***	0.98***	1.40***	1.64***
	(0.029)	(0.134)	(0.167)	(0.185)
Observations	1,255	1,255	1,255	1,255
Model	Linear Probability	Logit	Logit	Logit
Year fixed effects	N	N	Y	Y
Species fixed effects	N	N	N	Y
Antibiotic Status fixed effects	N	N	N	Y
Dispensing status fixed effects	N	N	N	Y

Column (1) is a simple linear probability with an intercept and a dummy variable for original drugs. In this simple framework, being an original drug nearly doubles the probability of having patent protection from 0.25 to 0.47. Columns (2)-(3) use a logit framework, adding in year dummies (column 3) and then species, antibiotic status and dispensing status dummies (column 4). In all cases, the impact of being original remains a highly significant positive predictor of patent protection. This provides some additional support that our designation "original" really is capturing novel R&D, compared to incremental R&D.

Does the value of incremental R&D decline in animal health?

Unfortunately, we have no data on product sales, and so we cannot directly assess the returns to increasingly incremental R&D. Instead, we use three proxies for the value of the patents associated with drugs to provide some (very tentative) evidence that the value of incremental R&D declines.

There are 468 patents associated with FDA approved drugs in our dataset. We assign each patent an "incremental R&D rank" (IRDR) score as follows. For every active ingredient:

- Find all associated drugs and order them by approval year.
- The first approved drug has an IRDR of 1, the second has an IRDR of 2, the third has an IRDR of 3 and so on. If multiple drugs are granted in the same year they are each assigned the same IRDR (i.e., if the first drug was granted in 2000 it has an IRDR of 1, but if two drugs were granted in 2001 they each have a score of 2).

A drug may have multiple IRDR's associated with different active ingredients, in which case we use the minimum for the drug. A patent's IRDR score is the average IRDR of the drugs it is associated with (we also control for the number of drugs a patent is associated with). We then look to see if a patent's IRDR score is negatively correlated with various proxies of value:

$$\text{patent value} \sim t + t^2 + (\#\text{ of drugs}) + (IRDR = 1) + IRDR \qquad (0.11)$$

For controls we include a quadratic time trend, based on a patent's grant year (we have too few observations to use yearly dummies), and the number of drugs the patent is associated with. Given that original drugs (IRDR = 1) have a disproportionate share of patents, it is not surprising

that many patents (48%) have an IRDR of 1. We separate these out by including a dummy variable for patents with an IRDR equal to 1. The mean IRDR is 2.5, with a standard deviation of 2.8.

We use three different proxies of value: renewal data, Kogan et al. (2017) estimates of patent value, and citations received within 5 years.

Renewal data provides our first proxy of value. Since 1980, US patent-holders have had to pay escalating fees to keep their patents in force after 4, 8, and 12 years. There is a large literature that uses patent renewal decisions as a proxy for the value of patents. This literature assumes a rational patent-holder will only pay for renewal if the value of continued patent protection exceeds the fee. We use an ordered logistic model (renewed to 4, 8, 12, 17 or 20 years) to assess whether patents with a higher IRDR are renewed less. Renewal data is only applicable to patents granted after 1980. Moreover, we exclude patents granted after 2004, because we need to wait 12 years to see if patents have been fully renewed. This leaves us 231 patents as observations.

Our second proxy of value is Kogan et al. (2017)'s estimates of the value of patents held by publicly traded firms. Kogan et al. (2017) base their estimates on the movements in market capitalization of the patent-holder in the three days before-and-after the patent's grant is announced. We use a simply OLS regression, with the log of patent value as the dependent variable. This data is available through 2010, but only the patents of publicly traded firms have associated estimates. This leaves us 199 observations.

Our final proxy of value is the number of citations received by a patent in the subsequent five years. There is a large literature that uses citations received as a proxy for patent value (Nagaoka, Motohashi, and Goto 2010). We use a simple OLS regression, with the log of the inverse hyperbolic sine transformation of citations.[1] To allow for five years of citation receipt, we exclude patents granted after 2010, leaving us 391 observations.

Reflecting the challenges of valuing patents, the correlation between these three measures is rather small (but positive): 0.11 between renewal and Kogan et al. (2017)'s estimates, 0.12

[1] This is a way to deal with 0 observations in a log setting. The inverse hyperbolic sine transformation of x is $x + (x^2 + 1)^{1/2}$, which converges to $2x$ for large values of x.

between renewal and citations, and 0.06 between the Kogan et al. (2017) estimates and citations. Table 2 displays our results.

Table 2. Incremental R&D Rank and the Value of Associated Patents

	Dependent variable:		
Depe	Renewals	log(Kogan et. al 2017 estimates)	log(HIS(citations))
t	-0.162	0.007	0.099***
	(0.085)	(0.048)	(0.021)
t^2	0.003	0.001	-0.002***
	(0.002)	(0.001)	(0.001)
IRDR = 1	2.319**	-0.424	0.114
	(0.778)	(0.251)	(0.119)
IRDR	0.060	-0.115*	0.031
	(0.078)	(0.049)	(0.021)
# of drugs	-0.117**	0.0002	-0.015*
	(0.040)	(0.011)	(0.007)
Constant		1.809***	0.174
		(0.407)	(0.195)
Observations	231	199	391
Model	Ordered Logistic	OLS	OLS
Adjusted R^2		0.196	0.065
Note:			*p<0.05; **p<0.01; ***p<0.001

We find some modest evidence that patents associated with more incremental R&D are worth less. Patents are more renewed if they have an IRDR of 1 than if they have an IRDR>1, but we cannot reject the null that beyond 1 a higher IRDR is uncorrelated with renewal. In contrast, a higher IRDR is correlated with a lower patent value, using Kogan et al. (2017)'s estimates, but we do not detect a discontinuity for IRDR = 1. Lastly, we cannot reject the null hypothesis that a higher IRDR is not associated with receipt of more citations within 5 years.

To summarize, we assigned each patent a score based on how "new" the active ingredients of the drugs it protects are. A patent protecting the 5th and 6th drugs to use some active ingredient has a higher score than a patent protecting the 1st and 2nd drugs to use an active ingredient. We find no evidence that the value of patents is positively correlated with this score, and some evidence that

patents with lower scores are more valuable. Given that our data is spotty and imprecise, we take this as tentative evidence for our assumption that the marginal value of incremental R&D declines in animal health.

4. Results

4.1 Baseline Results

We adopt two empirical strategies. First, because many drug categories frequently have zero approvals in a given year (especially for originals), we use a conditional logit specification, where the dependent variable is a binary indicator equal to 1 if the number of drug approvals in a particular year-category is greater than zero. We use the Chamberlain estimator to remove category fixed effects and additionally include dummies for each year.

Second, we follow the empirical strategy of Acemoglu and Linn (2004) and Branstetter, Chatterjee, and Higgins (2014) in modeling the number of drug approvals in a given year-category as a poisson process. Our baseline specification takes the form:

$$E[\, y_{ct} \,] = \exp(\, \alpha_c + \gamma_t + \beta_1 \cdot GenShare_{ct-1} \,) \tag{0.12}$$

where y_{ct} is the number of approvals in category c in year t. We use a poisson fixed effects estimator to remove category fixed effects α_c by conditioning on the total number of approvals in a given category (see Acemoglu and Linn 2004 for discussion) and include time fixed effects as dummy variables in the regression. Note the generic share (GenShare) in a category is lagged by one period, since y_{ct} affects the value of GenShare in period t.

Furthermore, each regression model is run twice, once with original drug approvals as the dependent variable and once with all non-generic drug approvals as the dependent variable. Table 3 presents our baseline results.

	(1)	(2)	(3)	(4)
Dependent Variable	Originals > 0	Originals	All > 0	All
GenShare	-5.77**	-4.68**	-1.28	0.16
	(1.87)	(1.52)	(1.21)	(0.65)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	280	-	739	-
Num. obs.	2226	2226	2226	2226
Log-Likelihood	-514.86	-763.05	-822.52	-1794.66

***p < 0.001, **p < 0.01, *p < 0.05

Table 3. Baseline Regressions

Models (1) and (2) correlate the flow of annual original drug approvals in a year with the share of active drugs that are generic. Models (3) and (4) correlate the flow of all non-generic drug approvals (original and incremental) with the share of active drugs that are generic. These results support our motivating model: while the total number of drugs is unchanged, the number (and therefore share) of original drugs is sharply curtailed in the presence of more generic competition. The impact of the generic share variable is both statistically and economically significant. We reject the null that the coefficient is equal to zero with *p*-value less than 0.01 in both the conditional logit and poisson specifications. Meanwhile, the estimated coefficient of -4.68 in model (2) implies moving from a generic share of 0 to 0.2 (the 2015 median) is associated with a 61% reduction in the annual flow of original drug approvals.

4.2 Variation Among Therapeutic Classes

In this section, we allow the coefficient on GenShare to vary by therapeutic class. Our results are displayed in Table 4.

	(1)	(2)	(3)	(4)
Dependent Variable	Originals > 0	Originals	All > 0	All
GenShare - Antibiotics	-6.26**	-5.76**	-1.20	0.06
	(2.18)	(1.92)	(1.26)	(0.66)
GenShare - Parasiticides	-7.83*	-5.66	-0.97	0.85
	(3.78)	(3.01)	(1.78)	(1.26)
GenShare - Other	-2.63	-1.98	-5.60*	-0.33
	(2.70)	(2.01)	(2.44)	(1.33)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	280		739	
Num. obs.	2226	2226	2226	2226
Log-Likelihood	-513.49	-760.89	-820.18	-1794.31

***p < 0.001, **p < 0.01, *p < 0.05

Table 4. Generic Share by Therapeutic Class Regressions

We find the correlation between GenShare and the flow of original drugs is strongly negative and statistically significant for antibiotics. In model (1), we also reject the null for the Generic Share of parasiticides at the 5% confidence level, though we can only do so in model (2) at the 10% level (*p*-value of 0.060). When turning to all drugs (models 3 and 4), in general we cannot reject the null that the true coefficient of GenShare is zero for any therapeutic class. There is one exception: in model (3) the coefficient on GenShare is negative and statistically distinct from zero at the 5% level, but this does not hold in model (4) (even at the 10% confidence level).

Generally speaking, we find a stronger correlation between GenShare and original drug approvals for antibiotics and parasiticides than for "other" drugs. We view this as consistent with our model. Our identification strategy assumes a higher share of generic drugs proxies for a higher probability that new products in the category will face a (possibly imperfect) substitute marketed at competitive prices. This mechanism will tend to be stronger in more narrowly defined drug categories because drugs in these categories have a higher probability of being substitutes for each other.

Antibiotics and parasiticides are almost certainly more narrowly defined than the "other" drugs category. The therapeutic category "other" is a residual formed from drugs that do not fit into

either of the other two categories. It is a more heterogeneous and diverse set. For example, in the category “other prescription drugs for hogs” we have drugs used to anesthetize, facilitate birthing, mitigate aggressive behavior, and to immunologically castrate. In contrast, all drugs in the therapeutic category “antibiotics” retard bacteria growth and all drugs in the therapeutic category “parasiticides” manage pest infestations in the relevant species.

4.3 Long-run

At the end of section 1, we presented reasons to believe the total supply of R&D might begin to decline in the long-run (though not the short-run), in the presence of negative profitability shocks. Essentially, our argument was that in the short-run, the stock of researchers with the requisite human capital to develop drugs in a particular sector is fixed, but they can allocate their energy to incremental or original R&D. In the long run, however, the stock of researchers ought to fall if R&D is less profitable in a category. In this section, we add the 10-year lagged value of GenShare to test this supposition. The results are presented in Table 3.

	(1)	**(2)**	**(3)**	**(4)**
Dependent Variable	Originals > 0	Originals	All > 0	All
GenShare	-6.02*	-4.89*	-0.50	1.07
	(2.41)	(1.95)	(1.39)	(0.73)
GenShare lagged 10 years	0.64	0.57	-2.19	-3.07*
	(3.75)	(3.17)	(2.08)	(1.33)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	280		739	
Num. obs.	2226	2226	2226	2226
Log-Likelihood	-514.85	-763.04	-821.97	-1791.95

***p < 0.001, **p < 0.01, *p < 0.05

Table 5. Incluing GenShare Lagged 10 Years Regressions

Adding the 10-year lag of GenShare makes our estimates of the impact on GenShare less precise (in models 1 and 2 we can only reject the null that the coefficients are equal to zero at the 5% confidence level). In models (3) and (4), the estimated coefficient of the lagged GenShare is negative and we can reject the null that it is equal to 0 in model (4) at the 5% confidence level

(*p*-value 0.021), but not in model (3). While this evidence does not disprove our supposition, neither is it particularly compelling.

4.4 Summary

The results of this section broadly support our motivating model. Generic competition is negatively correlated with the flow of *original* drugs in a particular category, but tends to have little or no effect on the *total* number (original and incremental) of drug approvals. This effect is strongest for more narrowly defined drug categories such as antibiotics and parasiticides than it is for the "other" drug category. Given our identification strategy, this is as we would expect: generic competitors are more likely to erode the profits of new drugs when those new drugs perform a similar function as the generic. Finally, we find some very modest evidence consistent with our supposition that the total number of drugs also declines in the long run.

One concern with these baseline results is that generic share may be endogenously determined. In particular, omitted variable bias represents a potential problem. It may be that pharma companies and their generic competitors each foresee that there will be fewer original drugs in some categories. If generic firms disproportionately enter these sectors (for example, because they know their generic versions will be good substitutes for the best drugs in the category if no new drugs are coming), then this would undermine our identification strategy. In particular, exogenous changes in scientific opportunity that vary across drug categories are a primary candidate for an important omitted explanatory variable. In the next section, we attempt to address this concern.

5. Addressing Endogeneity Concerns

To address potential endogeneity concerns with respect to the share of generic drugs in a category, we use two different proxies for scientific opportunity, and then a control function approach with the share of pre-1990 patented drugs as an instrument.

5.1 Post 1989 Dummy Variables

Our baseline specifications include drug category fixed effects, which suffice to control for time-invariant differences in the scientific opportunity across drug types. Our first approach adds additional controls for the period during which generic drug approvals are possible, in order to

allow scientific opportunity to vary a little across time. To our category and year fixed effects, we now add terms for species, interacted with a dummy for the post 1989 period. This controls for post 1989 changes in the average propensity to develop drugs for distinct species irrespective of generic penetration. We additionally add terms for therapeutic status, and dispensing status, interacted with both a dummy for the post 1989 period and a dummy for "food" animals (cattle, chicken, swine, and turkeys). This controls for any change in the average propensity to develop drugs of a given therapeutic class or dispensing status after 1989, and allows for differences between animals raised for consumption and those raised as companions. These variables would also control for broad changes in scientific opportunity after 1989 at the level of species, therapeutic classes (in companion or food animals) and dispensing status (in companion or food animals). Table 6 displays these results.

While these additional controls are frequently statistically significant, they do not substantively change our results for original drugs. Both estimated coefficients negative and statistically and economically significant. The inclusion of these variables has a larger impact on the estimated coefficient in models (3) and (4). We still cannot reject the null that the coefficient on GenShare in model (3) is zero, but this null is rejected at the 5% significance level in model (4) (the poisson model). That said, the impact is less economically significant than in for original drugs: a move in the Generic share from 0 to 0.2 is associated with a 31% reduction the annual production of non-generic drugs compared to a 55% reduction in model (2).

	(1)	(2)	(3)	(4)
Dependent Variable	Originals > 0	Originals	All > 0	All
GenShare	-5.05*	-3.95*	-2.60	-1.84*
	(2.13)	(1.75)	(1.34)	(0.85)
post89-cattle	-0.04	0.09	1.41	2.06***
	(1.04)	(0.85)	(0.74)	(0.40)
post89-chickens	-0.22	0.00	0.94	2.01***
	(1.06)	(0.85)	(0.79)	(0.41)
post89-dogs	0.80	0.56	0.33	0.32
	(0.53)	(0.32)	(0.48)	(0.22)
post89-horses	-0.38	0.03	-0.27	0.05
	(0.59)	(0.39)	(0.56)	(0.27)
post89-swine	0.66	0.87	1.36	1.51***
	(1.03)	(0.86)	(0.72)	(0.41)
post89-turkeys	0.20	0.50	2.00**	2.43***
	(1.22)	(1.00)	(0.75)	(0.46)
post89-other	0.61	0.61	-1.31*	0.38
	(0.54)	(0.31)	(0.66)	(0.22)
post89-para	1.04	1.27**	1.77***	1.69***
	(0.61)	(0.48)	(0.46)	(0.29)
post89-RX	0.67	0.44	0.35	0.90***
	(0.63)	(0.52)	(0.43)	(0.27)
post89-other-food	-1.22	-1.25*	0.13	-1.14***
	(0.78)	(0.58)	(0.78)	(0.31)
post89-para-food	-0.09	-0.56	-1.91**	-1.77***
	(1.09)	(0.96)	(0.66)	(0.40)
post89-RX-food	0.88	1.17	0.12	-0.58
	(0.86)	(0.74)	(0.60)	(0.36)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	280	-	739	-
Num. obs.	2226	2226	2226	2226
Log-Likelihood	-501.26	-744.53	-792.83	-1758.61

***p < 0.001, **p < 0.01, *p < 0.05

Table 6. Additional Controls Regressions

5.2. Original Drug Stock

Our second approach constructs a proxy for category-specific knowledge that we call the Original Stock by summing the preceding 10 years of original drug approvals, which we then

include with a one-year lag in our baseline regressions. We also experimented with windows less than 10 years, but these did not impact our results. The intuition is that scientific opportunity in a given drug category may change over time with a correlated component. We use the number of original drug approvals as our proxy for time-varying scientific opportunity, since we believe original drugs (rather than all drugs) are more closely related to scientific breakthroughs. Table 7 displays these results:

	(1)	**(2)**	**(3)**	**(4)**
Dependent Variable	Originals > 0	Originals	All > 0	All
Original Stock	-0.04	-0.04*	0.14***	0.01
	(0.03)	(0.02)	(0.04)	(0.01)
GenShare	-6.30**	-5.76***	-0.86	-0.15
	(1.93)	(1.64)	(1.29)	(0.66)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	189		562	
Num. obs.	1764	1764	1764	1764
Log-Likelihood	-365.05	-496.72	-619.79	-1321.57

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 7. Original Stock Regressions

Note our sample size is smaller because we require 10 years of lagging data to generate the Original Stock variable. The Original Stock is occasionally statistically significant in its own right. The coefficient is negative in model (2), consistent with a “fishing out” mechanism whereby at any moment there are only a finite number of original drug candidates, and these are more likely to be exhausted if there have been more original approvals recently. The coefficient is positive and highly significant in model (3), consistent with our view that original drugs provide a platform for subsequent elaboration.

However, our core results are mostly strengthened by the inclusion of the Original Stock variable. In models (1) and (2) the estimated coefficients on GenShare remain statistically and economically significant, while the estimated coefficients in models (3) and (4) continue to be indistinguishable from 0 at the 5% significance level.

5.3. Control Functions

Our final approach uses a control function to control for potential endogeneity. Control functions use a two-stage estimation procedure to generate a new explanatory variable that can control for the endogeneity of a variable, in some settings (see Wooldridge 2015 for discussion). The key assumption is the existence of a good instrument which is correlated with the potentially endogenous variable (in our case, Generic Share), but exerts no causal influence on the dependent variable, except through its impact on the endogenous variable. We use the share of drugs approved prior to 1990 with no *potentially* active patents applied for before 1989 as our instrument.

Because generic drugs can only be introduced for off-patent approved drugs, the extent to which the drugs in a given category have no active patents serves as a measure of how susceptible a category is to generic competition. However, the share of drugs in a category that are patented is itself endogenous. For our instrument to be valid, we require the share of drugs that are patented in a category be uncorrelated with the flow of drug approvals in that category, except through its impact of generic drugs. Because generic drugs were only feasible after 1989, we can test this assumption econometrically for the period prior to 1990. We use the same methods to model the flow of drug approvals, but with a category's patent share now included as an explanatory variable and restricting our analysis to years prior to 1990:

$$y_{ct} \sim f\left(\alpha_c + \gamma_t + \text{Original Stock} + \text{Unpatented Share}_{ct-1}\right) \quad (0.13)$$

Unpatented Share is defined as the share of all drugs in category *c* approved in year *t* or earlier without an associated patent. Note that we include the Original Stock variable, because in section 4.2.2 we showed it is sometimes statistically significant, and it is correlated with Unpatented Share (since original drugs are more likely to be patented). This validation exercise is reported in Table 8.

	(1)	(2)	(3)	(4)
Dependent Variable	Originals > 0	Originals	All > 0	All
Original Stock	-0.06	-0.06*	0.04	0.00
	(0.04)	(0.03)	(0.07)	(0.01)
Unpatented Share	-0.74	-0.45	-1.17	0.21
	(1.29)	(1.09)	(0.91)	(0.51)
Model	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y
Num. events	95	-	319	-
Num. obs.	672	672	672	672
Log-Likelihood	-170.33	-221.67	-215.62	-653.44

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 8. Pre-1990 Patent Share Validation

For the period prior to the introduction of generic drugs, we cannot reject the null hypothesis that Unpatented Share is not correlated with the annual flow of drug approvals in a category. This provides support for the key assumption that the share of patents in a category is not correlated with drug approvals, once the generic competition channel is removed.

That said, this validation exercise is performed only on the period preceding 1990. After 1990, patenting behavior may well have changed, because active patents preclude generics. For this reason, we construct our instrument from patenting behavior initiated prior to 1990. However, even this approach might be problematic if there is a major change in patenting behavior in anticipation of generic entry. This might manifest, for example, in an increase in the propensity to patent in the years right before 1990 (when it has perhaps become clear the 1988 Generic Animal Drug and Patent Term Restoration Act is likely to pass).

In Figure 1, we compute the annual probability that a drug approval has an associated patent for both original and incremental drugs. As is clear from the figure, there appears to be no discrete change in the probability of patenting in the years prior to 1990, but rather a continuous (but noisy) increase in the probability of patenting over most of our observation period. We take this as supporting evidence that our instrument is valid.

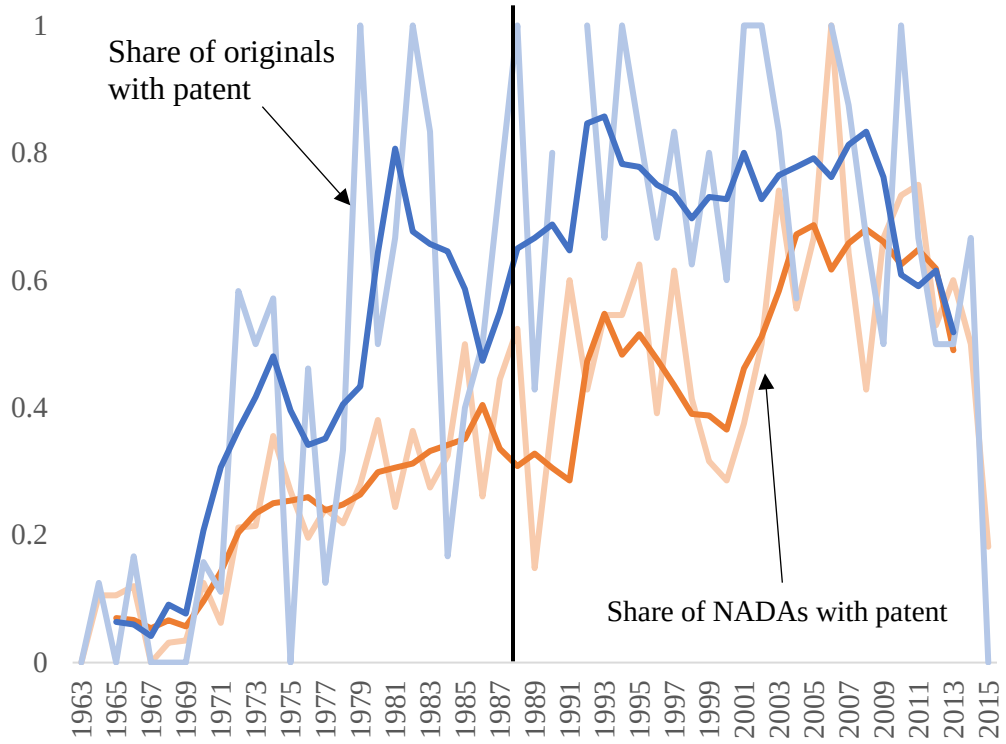

Figure 1. Share of annual drug approvals (original and NADAs) with patents. Dark lines correspond to centered 5-year moving average. Vertical line at 1988.

Our first stage regression is an OLS regression of the form:

$$GenShare_{ct-1} = 0 + 1(year > 1988) \cdot (\alpha_c + \gamma_t + \beta_1 \cdot \text{Original Stock}_{ct-1} + \beta_1 \cdot \text{pre89 unpatented}_{ct}) + v_{ct} \quad (0.14)$$

Where 1(·) denotes a dummy variable. For any observation in year 1988 or earlier, the Generic Share must be zero, since generic drugs did not exist at this point. For observations after 1989, we use our standard category fixed effects and annual dummies, the Original Stock, and we add the instrument "pre89 unpatented."

The pre89 unpatented variable is constructed as follows. First, gather the set of all drugs in category *c* approved prior to 1989. Let us assume there are n_c such drugs. For each of these drugs, we assume it might have an active patent in year *t* if (1) there was a patent application associated with the drug filed before 1989 and (2) less than 18 years have elapsed since the patent was granted. For example, suppose NADA 123-456 was approved in 1985, and an

associated patent was filed in 1986. The patent wended its way through the patent office and was finally granted in 1988. Prior to 1995, US patents had a 17 year life. So we assume NADA 123-456 *might* have an active patent protecting it until it's patent expired in 2005. We therefore assume NADA 123-456 *might* enjoy patent protection over the period 1985-2005. When a NADA has multiple patents (with applications filed before 1989) associated with it, we use the latest grant year plus 17 years to define the end of patent protection.

Note that we consider a drug protected even if a patent was granted after the drug was approved, because we assume the threat of a pending patent dissuades generic competitors (at any rate, most patents applied for before 1989 were granted before generic competition set in in 1992). Furthermore, a patent might not actually be active for the full 17 years if the patent-holder decides not to renew the patent. We do not exploit patent renewal data here because the decision to renew after 1990 may be endogenously responding to the threat of generic competition. Instead, we mechanically assume patents might last 17 years. In each year, let the number of NADAs granted before 1989 with potentially active patents be p_{ct}. We define the pre89 unpatented variable as:

$$\text{pre89 unpatented} = 1 - \frac{p_{ct}}{n_c} \tag{0.15}$$

Thus, pre89 unpatented is a proxy for the share of drugs in category *c* that are vulnerable to generic copying in year *t*. We restrict our control function regressions to the period for which there is cross-category variation in pre89 unpatented. Because patents last 17 years, no patents granted before 1989 are still active past 2005. However, we still have variation in pre89 unpatented as late as 2011, because some patent applications filed before 1989 were not granted until 1994. Thus, our second-stage regressions cover the period 1963-2011. Our first stage results are displayed in column (0) of Table 9.

Our second stage regressions then add the residuals from the first stage regression as an additional explanatory variable. Loosely speaking, they can be considered the "endogenous component" of GenShare, since they are the part that cannot be predicted from the explanatory variables of equation (0.14). If these residuals are statistically significant, it can be interpreted as a test of endogeneity. The results of our second-stage regressions are displayed in Columns (1)-(4) of Table 9.

	(0)	(1)	(2)	(3)	(4)
Dependent Variable	GenShare	Originals>0	Originals	All>0	All
pre89 unpatented	0.05*				
	(0.02)				
Original Stock	-0.01***	-0.05	-0.05**	0.13***	0.01
	(0.00)	(0.03)	(0.02)	(0.04)	(0.01)
GenShare		-10.38***	-9.13***	-2.22	-0.27
		(2.99)	(2.39)	(2.21)	(0.88)
First Stage Residuals		7.00	6.23*	1.74	1.40
		(3.72)	(2.84)	(2.81)	(1.43)
Model	OLS	Logit	Poisson	Logit	Poisson
Category Fixed Effects	Y	Y	Y	Y	Y
Time Fixed Effects	Y	Y	Y	Y	Y
Num. events		173		525	
Num. obs.	966	1596	1596	1596	1596
Log-Likelihood	1394.35	-338.88	-459.35	-563.64	-1239.86

***p < 0.001, **p < 0.01, *p < 0.05

Table 4. Control Function Regressions

Beginning with column (0), our instrument pre89 unpatented is positive, as we would anticipate (a higher share of unpatented drugs in a category is associated with more generic competition), and we reject the null that the true coefficient is 0 (*p*-value is 0.015). The F-statistic for the joint significance of all coefficients is 31.7 with 65 and 900 degrees of freedom. We also find the original stock is negatively correlated with the generics share, so that categories with more original drugs face less generic competition, implying this is an control variable.

Turning to our second stage regressions, our control function exercise strengthens our baseline findings. Once again, the impact of GenShare on original drug approvals is negative, and statistically and economically highly significant (indeed, more so than in any other regression). Moreover, we continue to fail to reject the null hypothesis that GenShare has no impact on the total number of drug approvals.

In one of our four specifications (model 2), the first stage residuals are statistically significant with a *p*-value equal to 0.028. In the remaining three, we cannot reject the null hypothesis that the residuals have a coefficient of 0 with a 5% confidence level. This provides some inconclusive evidence that controlling for the endogeneity of generic share is important.

6. Conclusion

When faced with new competition, research-intensive firms are likely to change the kind of research they undertake. We consider a model where firms have relatively fixed research assets (which we argue is a reasonable assumption in the short-run), and where original research is more costly than incremental research. The optimal allocation of incremental R&D per product line, in this setting, equates the marginal value of incremental R&D to the average rate of return on starting a new product line, with return at each moment in time weighted by the discount rate. As an aside, when researchers do not discount, our results converge to those of Charnov (1976), a classic paper in ecology. We show that in the presence of a negative profit shock or a positive shock to the cost of original R&D, firms respond by increasing time spent on incremental R&D per original product.

These predictions are borne out in our study of the animal health industry. Using a dataset of every approved animal drug from 1962-2015, we divide drugs into 42 categories based on the species, dispensing status, and therapeutic class of the drug. We then assess the impact of generic drug entry, which became legal in 1989, in each category. Generic entry does not tend to be correlated with the flow of all annual drug approvals. However, beneath these aggregate summaries, large effects are taking place. In our baseline estimate, moving from no generic competition to the median results in a 61% decline in the annual number of original drug approvals (those with a new active ingredient). This decline, however, is offset by an increase in incremental drug approvals.

Original drugs appear to be important: they are significantly more likely to be patented, and we find some evidence the associated patents are more valuable. The impact of generic competition on original drugs tends to be largest for the most narrowly defined drug categories (where we would expect substitutability to be highest). It is robust to the inclusion of additional controls, such dummy variables that allow for changes in technical opportunity during the period generic drugs entered, and a measure of lagged original drug development.

Our paper also attempts to control for the endogeneity of generic drug entry by using the share of drugs with potentially active patents initiated before generic drug legislation. We show this instrumental variable is uncorrelated with our dependent variable during the period preceding generic drug legislation, and that it is correlated with generic share. We use this instrument in the

first stage of a control function regression, and include the first-stage residuals as an additional explanatory variable in the second stage. Our results are robust to the inclusion of these residuals (and indeed, we find our largest coefficients in this specification).

Nonetheless, our work certainly faces limitations on both empirical and theoretical grounds. On the theory side, our motivating model could be extended to allow firms to respond to competition by developing drugs that are differentiated from those sold by generic entrants. We have implicitly assumed drug categories are so narrow that there is little scope for this, but it this is an avenue potentially worth exploring. Meanwhile, while we have a rich dataset on the characteristics of approved drugs, we lack much desirable data that could further strengthen our paper. We do not observe the original drug sponsors, only the sponsors as of when we collected our data in 2016. This prevents us from including firm fixed effects in our data. Given the absence of firm data, we also lack data on R&D spending by firms, and sales by drugs. Both of these could further clarify the interpretation of our results.

Our results have several implications for policy. First, our results are most directly relevant for understanding policies that impact the animal pharma sector. The strong impact of generic competition on original drug development may suggest innovation in animal pharma is unusually sensitive to the length of patent protection and market exclusivity. This may be a potential lever to induce innovation in desired drug categories, such as those that can substitute for some of the functions of antibiotics.

Second, in the broader literature of health, our results starkly illustrate the trade-off between ex-ante and ex-post welfare that is posed by generic drug programs. Notably, we appear to find a substantially larger negative impact of generic drug entry than Branstetter, Chatterjee, and Higgins (2014), who look at the human pharma sector. They find an elasticity of 0.79 with respect to the share of generics in a category (defined in terms of sales, not approvals though), compared to our findings in the range of 4-9. There are of course many differences between human and animal pharma, but one important one is the absence of third-party intermediaries, which may make consumers highly sensitive to prices. If this is the case, it may be the impact of generic entry is stronger in animal pharma than in human pharma.

Finally, when evaluating the impact of a policy or competitive change on innovation, it is important to look at the kind of innovation as well as the total amount. In our setting, original

R&D tends to be both more expensive and more valuable than incremental innovation, and so the strongly negative effects of the policy are notable, even if total drug approvals are unchanged. This is potentially relevant for other shocks to firm profitability beyond generic drug policy, including anti-trust policy, international trade, and regulatory burden.

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Appendix: Antibiotic Assignment

To assign drugs to antibiotic status, we first perform exact character value matching of the listed ingredients to four lists of antibiotics from external sources. These sources are:

1. The World Health Organization's list of "Critically Important Antimicrobials for Human Medicine" (2017).
2. The U.S. FDA's Guidance for Industry 152 (2003b).
3. The U.S. FDA's reports on using the information from the Animal Drug User Fee Act report (U.S. FDA 2017b)
4. The OIE list of antimicrobials of veterinary importance (undated).

We also supplement the list of "not medically important" antibiotics with information from various extension services that reported on impacts of the recent Guidance for Industry 213, which regulated medically important antibiotics.

The OECD's list is notably a list of veterinary *antimicrobials*, thus it includes more than just *antibiotics* (antibiotics are technically a subset of antimicrobials, even though the two terms are often used interchangeably). We therefore find matches first using the WHO and FDA lists. If an ingredient is matched to the OECD list but not the WHO and FDA lists, we manually check it. In some cases these ingredients were non-antibiotic antimicrobials, but in others they were also antibiotics. The use of multiple lists is important because there are slight variants to many names of antibiotics. We also find phonetic matches (for example, to match "cephalexin" with "cefalexin"). We manually check the matches, and then manually check the non-matched ingredients. An entire list of antibiotic ingredients are found in Appendix Tables 1 and 2.

Appendix Table 1: Medically important antibiotic ingredients in approved FDA-CVM products

amikacin sulfate	cloxacillin benzathine	orbifloxacin	sulfadiazine sodium
amoxicillin trihydrate	cloxacillin sodium	ormetoprim	sulfadimethoxine
ampicillin anhydrous	danofloxacin	oxytetracycline	sulfaethoxypyridazine
ampicillin sodium	dicloxacillin sodium monohydrate	oxytetracycline (monoalkyl trimethyl ammonium salt)	sulfamerazine
ampicillin trihydrate	difloxacin hydrochloride	oxytetracycline dihydrate	sulfamethazine
apramycin sulfate	dihydrostreptomycin	oxytetracycline hydrochloride	sulfamethizole
benzylpenicillin	dihydrostreptomycin sulfate	pencillin	sulfanitran
carbomycin	doxycycline hyclate	penicillin	sulfaquinoxaline
cefadroxil	enrofloxacin	penicillin g	sulfathiazole
cefovecin sodium	erythromycin	penicillin g benzathine	sulfisoxazole
cefpodoxime proxetil	erythromycin phosphate	penicillin g potassium	sulfomyxin
ceftiofur crystalline free acid	erythromycin thiocyanate	penicillin g procaine	tetracycline
ceftiofur hydrochloride	florfenicol	penicillin v potassium	tetracycline hydrochloride
ceftiofur sodium	furazolidone	pirlimycin hydrochloride	tetracycline phosphate
cephalexin	gamithromycin	polymyxin b sulfate	ticarcillin disodium
cephalonium	gentamicin sulfate	pradofloxacin	tildipirosin
cephalothin	hetacillin potassium	pyrimethamine	tilmicosin
chloramphenicol	kanamycin sulfate	sarafloxacin hydrochloride	tilmicosin phosphate
chloramphenicol palmitate	lincomycin	spectinomycin dihydrochloride pe	trimethoprim
chlortetracycline	lincomycin hydrochloride	spectinomycin hydrochloride pentahydrate	tulathromycin
chlortetracycline bisulfate	lincomycin hydrochloride monohydrate	spectinomycin sulfate tetrahydrate	tylosin
chlortetracycline calcium complex	marbofloxacin	streptomycin	tylosin phosphate
chlortetracycline hydrochloride	neomycin palmitate	streptomycin sulfate	tylosin tartrate
clindamycin	neomycin sulfate	sulfachlorpyridazine	tylvalosin tartrate
clindamycin hydrochloride	oleandomycin	sulfadiazine	virginiamycin

Appendix Table 2. Not currently medically important antibiotic ingredients in approved FDA-CVM products

avilamycin	carbadox	monensin usp	novobiocin sodium
bacitracin methylene disalicylate	laidlomycin propionate potassium	mupirocin	nystatin
bacitracin methylenedisalicylate	lasalocid	narasin	salinomycin sodium
bacitracin zinc	monensin	nitrofurantoin	semduramicin sodium
bambermycins	monensin sodium	novobiocin	tiamulin
			tiamulin hydrogen fumarate