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# **Incentivizing New Veterinary Pharmaceutical Products to Combat Antibiotic Resistance**

**Matt Clancy**  
**Economic Research Service, USDA**  
**Matthew.clancy@ers.usda.gov**

**Stacy Sneeringer**  
**Economic Research Service, USDA**  
**ssneeringer@ers.usda.gov**

## **Abstract:**

The development of new health products is one way to reduce antibiotic use in food animal production. Programs to incentivize research and development (R&D) for human drugs have been adopted, and government bodies have recently called for such a program in veterinary pharma. However, little research has been devoted to such mechanisms for animal pharma. We describe the broad “push” and “pull” incentive mechanisms for human pharma, and analyze the differences in employing these in veterinary pharma. Using newly compiled data on veterinary drug approvals, we estimate the “push” costs of R&D per approval. Using market size by species and approvals, we estimate the “pull” costs of incentivizing a new drug.

**Keywords:** Agriculture, antibiotics, innovation, pharmaceutical markets, incentives, drugs

**JEL Codes:** Q1, L1, O3, L65

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

Antibiotics are one of our most important tools for improving health, but their continued efficacy is not guaranteed. The U.S. Centers for Disease Control and Prevention (CDC) estimate that over two million people in the U.S. become ill each year from antibiotic resistance infections, with at least 23,000 dying (CDC, 2013). With the discovery of gene strains with resistance to the antibiotic colistin in 2015 (Liu et al. 2016), the prospect of bacteria that do not respond to any antibiotics in our arsenal looms. Meanwhile, the development of novel antibiotics to restock our supply has slowed significantly over the last several decades (Katz et al. 2006, Outterson et al. 2013).

Antibiotics are widely used in both human health and livestock production (Sneeringer et al, 2015), but any use (by humans or animals) can encourage antibiotic resistance that imposes large costs on society not borne by the user (O'Brien, 2002; U.S. CDC, 2013). This negative externality presents a case for government intervention.<sup>1</sup> While the science directly connecting onfarm antibiotic use to clinical human infections or the spread of resistant genes is ongoing, policy makers have adopted and encouraged regulations to reduce antibiotic use as an initial method of combating resistance (Shryock and Richwine 2010; U.S. FDA, 2012 and 2013).<sup>2</sup>

One shortcoming of relying on regulations is that the restriction of inputs will generally increase the cost of outputs. If farmers are rational, limiting the use of antibiotics in animal agriculture will raise production costs (although these costs may be small for some policies – see Sneeringer et al. 2015). Moreover, this approach is less effective in combating antibiotic resistance when it is not embraced globally. Fast growing medium- and low-income countries

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<sup>1</sup> McNamara and Miller (2002) lay out the social welfare framework showing that private consumers will consume more antibiotics than are optimal from the social planner's perspective. Secchi and Babcock (2002) model effectiveness of antibiotics as a nonrenewable resource to examine optimal use of antibiotics in the human medical and veterinary sectors.

<sup>2</sup> There are also policies to reduce the improper use of antibiotics in human health, but they are not the focus of this paper.

combine rising demand for animal products with fewer restrictions on antibiotic use and relative consumer insensitivity to the use of antibiotics (Van Boeckel et al, 2017). It may well be that rising demand from medium- and low-income countries for food produced with antibiotics offsets any reductions of use in high-income countries.

As an alternative method of reducing agricultural antibiotic use, policy-makers have begun to consider policies to incentivize the development of new health products by the animal pharmaceutical (AP) sector. In September 2017, the U.S. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) released a draft report calling for such a program (PACCARB 2017). These new health products could be vaccines or better diagnostic tests that reduce demand for food-animal use of antibiotics, or new alternatives to antibiotics.<sup>3</sup> New products can raise productivity in animal agriculture, and if their price is low enough, could reduce antibiotic use in medium- and low-income countries (even if this is not a goal of these countries' regulators. Market availability of these products means social planners would be less reliant on regulatory institutions to reduce antibiotic use in agriculture.

Research and action on incentivizing new health products for human health is wide and deep (e.g., Sharma and Towse, 2011; Outtersson et al., 2015; Outtersson, 2014; Kremer and Glennerster, 2004; Rensick, Brogan, and Mossialos, 2016). However, analogous literature and programs for animal health products is nearly non-existent – indeed, one of PACCARB's main

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<sup>3</sup>Presumably incentives would only be directed at R&D for new veterinary products that would not contribute to antibiotic resistance. Thus we are generally not considering the incentivization of new antibiotics that would be used in human and animal medicine, although we discuss the potential for a drug to fail in the human drug development process and be moved to the AP market. The literature on promoting R&D for new human-use antibiotics grapples with how to incentivize a drug that would be rarely used, as widespread use would lead to resistance and decrease its own efficacy. This concern adds a layer of complexity that we avoid in this paper.

recommendations was to establish an institute to study the issue.<sup>4</sup> This paper attempts to begin filling this research gap.

We begin by briefly describing our research methods and data (Section 1). We next provide a qualitative description of the drug development and marketing process in AP, particularly in relation to human pharma (HP) (section 2). We introduce a simple framework of research and development (R&D) for drugs, applicable to either human or animal pharma (section 3). The framework parameters delineate the “push” and “pull” mechanisms used to incentivize new drug development. We use this framework to discuss market value, R&D costs, and probability of success differ across HP and AP, as an introductory assessment of the efficacy of employing HP incentive schemes in an AP context (section 4). We then turn to quantitatively estimating the cost of R&D per new drug approved in AP as an initial estimate of a “push” amount (section 5), then use lagged market size correlations species-specific drug approvals to estimate a “pull” incentive (section 6). We consider how the linkages between the human and animal R&D processes may impact incentive programs (section 7). We conclude with a discussion of questions in need of further research (section 8).

## **1. Methods and Data**

There is virtually no academic literature on the AP sector, let alone incentivizing the industry to generate goods deemed desirable for social welfare. Therefore, to inform this paper we rely on interviews; published statistics on the structure, organization, and attributes of the human and animal drug industries; and data we gathered through company reports and drug approval listings.

### *Interviews*

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<sup>4</sup> A notable exception in the economics literature that describes the animal pharmaceutical market is Buhr, Holtkamp, and Sornsen (2011).

We conducted an extensive set of interviews with animal health industry stakeholders, academic researchers, and Federal regulators. These were conducted between late 2015 and early 2016, and were initiated through cold calls, peer contacts, or meetings initiated at the National Institute for Animal Agriculture's Antibiotic Resistance Symposium in 2015. The interviews generally lasted between one and three hours; many involved multiple high-level representatives from individual pharma companies. To ensure confidentiality, we did not record these interviews. We did not collect numeric data from interviewees. The goal of these interviews was largely to understand the players in, structure of, and incentives motivating the industry; this is all information unavailable in printed text, either in scholarly publications or online. After our initial interviews we organized a public conference at which many of the interviewees spoke; their presentations can be found at <http://www.farmfoundation.org/webcontent/Presentations-from-Incentives-Disincentives-to-R-D-Workshop-1926.aspx>. These presentations serve as external documentation of many of the interviewees' statements.

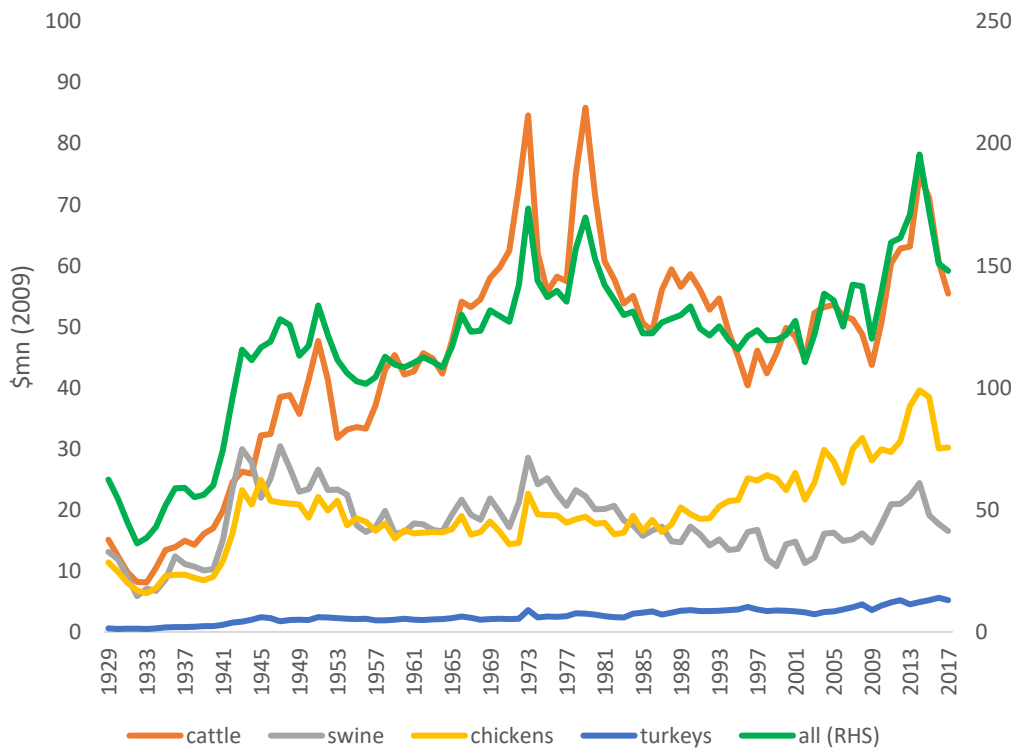
### *Data Collection*

In addition to published statistics available through a variety of sources, we gathered our own data. First, we developed our own dataset on veterinary pharma product approvals from 1940 through 2015. Veterinary drug approvals is overseen by the FDA's Center for Veterinary Medicine (CVM). To create a database of drug approvals, we text-scrape scanned images of Greenbooks, the annual listings of drug approvals published by CVM. In each year after 1990, the annual Greenbook provides a list of all new drugs approved in that year. The 1989 Greenbook lists all approvals prior to 1989 and the year of approval. Next, we supplement the Greenbook data by web-scraping the CVM's webpage listings of drug approvals; this provides information sometimes not found in the Greenbooks.

Second, we examine annual company reports to ascertain sales and R&D expenditures. Occasionally these also gave us information on sales for high-selling products and percentages of sales in antibiotics. In conjunction with the approval data, we use the R&D expenditure data to examine research costs per approval.

Third, we use estimates of commodity cash receipts, measured in real 2009 dollars, by the USDA Economic Research Service as our metric for the value of animal markets. We take the USDA’s “Cattle and calves” series for the cattle market and the “hogs” series for the swine market. For the Turkeys market, we use the NASS series for annual production value of turkeys, deflated by the same price deflator to convert into 2009 dollars. For the chickens market, we subtract our estimate for the Turkey market from the USDA’s poultry series. In some specifications, we also include total cash receipts across all of US animal agriculture as an additional control.

**Figure 1. Cash Receipts (Real 2009 Dollars) by Commodity**



Source: USDA ERS. The 2016 and 2017 figures are forecasts.

Figure 1 displays three-year moving averages of the annual cash receipts in 2009 dollars by commodity group. Notably, total animal and animal product cash receipts surged over the same period that drug approvals surged. Otherwise, there is significant heterogeneity by species.

## **2. Drug Development and Marketing in Human and Animal Pharma**

AP and HP share many features, and therefore an incentive program in AP is likely to share similar features to one in HP. Both industries are R&D intensive; the ratio of R&D to sales was 7.8% in AP in 2007 (Fuglie et al. 2011, pg. 86) and 12.7% in HP (National Science Foundation 2010, Appendix Table 4-14). For comparison, R&D's share of GDP was 2.6% in the same year (National Science Foundation 2016, Appendix Table 4-1). 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 HP, prescriptions or veterinary feed directives from veterinarians in AP). Indeed, so similar are the businesses that six of the top seven largest companies selling animal drugs are divisions of HP companies (see Table 1). The exception is Zoetis, which was itself a division of the HP 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.



**Table 1: Major Animal Pharmaceutical Companies' Sales, 2014**

<b>Parent Company</b>	<b>Animal Health Divisions</b>	<b>Sales (M\$)</b>	<b>Animal Health Sales (M\$)</b>	<b>Share of Animal Health Sales in Parent Total (%)</b>
Zoetis	-	4,785	4,785	100%
Merck	Merck Animal Health	42,237	3,454	8%
Sanofi	Merial	40,862	2,512	6%
Eli Lilly and Company	Elanco	19,616	2,347	12%
Bayer	Bayer Animal Health	54,153	1,690	3%
Boehringer-Ingelheim	Various	16,114	1,367	8%
Novartis	Novartis Animal Health Division	57,996	1,174	2%
Virbac	-	935	935	100%
CEVA	-	926	926	100%
Phibro	-	749	698	93%

Source: ERS, USDA, from information gathered from company reports.

\*Novartis animal health acquired by Eli Lilly in January 2015

While AP is a large global presence, it is small in comparison to HP (Table 2). In 2014, HP realized over one trillion dollars in global sales, 50 times that of AP sales (\$23.9B). The ratios for North America are similar. A “blockbuster” drug in human health generates \$1 billion per year, whereas in animal health a “blockbuster” drug generates \$100 million per year (Hunter 2016).

**Table 2: Human versus Animal Pharmaceutical Industry Sales, 2014**

	<b>Human</b>	<b>Animal</b>	<b>Ratio of Animal to Human</b>
Global	\$1,057.1B	\$23.9B	2%
North America	\$406.2B	\$7.9B*	2%

Source: Human data from IMS Health Market Prognosis, 2015; and IMS Health MIDAS, 2014. Animal data from 2014 and 2013 IFAH annual reports (IFAH 2015a, 2014).

\*Estimate based on IFAH report of total sales and percentage in North America.

Drug development in animal health follows a similar pathway as in human health; for exposition we divide this pathway into two broad stages based on applicability to one or both

markets. The first stage is discovery, in which new chemical compounds are first identified and screened for useful effects. During this phase, drug companies determine whether a compound meets a set of desirable criteria such as therapeutic efficacy, ease of manufacture, stability, safety, eligibility for intellectual property rights, and so on. Which chemicals are tested is guided by market considerations as well as existing knowledge of biological and chemical pathways. During the discovery stage, the relevant biological and chemical knowledge in the animal health industry has substantial overlap with the knowledge base used in human medicine.

While testing of compounds may begin in computer modeling or in vitro experiments, it then proceeds to in vivo (in animal) testing. For drug candidates targeted for either the human or animal markets, these tests may use similar animals, such as rodents. That said, the kind of tests required for each market do vary and are not perfect substitutes. Nevertheless, testing may provide useful information for both human and veterinary applications.

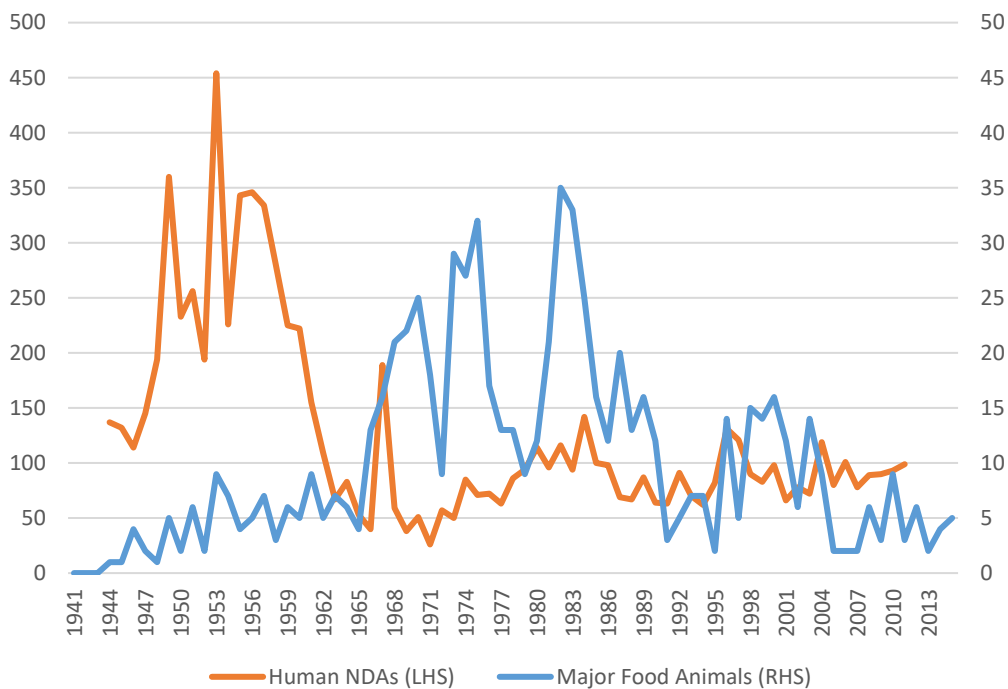
The compounds that do not fail to pass discovery proceed to the second stage of the drug development pathway: registration. This stage entails extensive testing required to receive approval to market a drug from the relevant national regulatory authority, as well as logistical considerations for demand, manufacturing, and marketing. Passing through the regulatory pathways is separate but similar for human and veterinary drugs. In the USA, non-biologic drugs for animals must seek approval from the FDA, just as human drugs must. Tests will generally need to prove a drug is effective, that it can be manufactured according to best practices, and that it is safe; in the case of AP, 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.

Although animal drug development reportedly costs substantially less than human drug development, getting a drug to market still costs millions of dollars. Exacerbating these financial

barriers is the time required to realize all the value of a given drug. Given the small size of the market, this creates significant barriers to entry, leading to a more concentrated market. The top 8 AP firms account for 76.4% of sales, compared to 49.6% for the entire pharmaceutical and medicine manufacturing sector.<sup>5</sup>

The high cost to bring a new drug to market also significantly restricts the number of products put on the market, relative to human health. Figure 2 displays the annual number of new drug approvals (NDAs) from the FDA for humans and major food animals (cattle, swine, sheep, chickens, and turkeys). The right axis, which corresponds to drug approvals for major food species, has a scale 1/10 the left axis, which corresponds to human drugs.

**Figure 2. Annual Drug Approvals by the FDA for Humans and Major Food Animals**



Source: FDA (2013) and FDA Green Books

<sup>5</sup>Notably, the statistic for the entire pharmaceutical and medicine manufacturing sector comes from 2007, arising from the 2007 Census, the latest figure available for this sector. The AP number is for 2014.

HP and AP parallel and overlap in the innovation process to bring new drugs to market, but they also adopt similar methods to protect their intellectual property. Both HP and AP make extensive use of patents (Arora et al 2008; Cohen 2010), which provide exclusive control of a drug for 20 years. When patents expire, in both industries there is a process in place for new entrants to receive marketing approval for generic versions of the previously patented drug. Firms must demonstrate their drug is bioequivalent, but do not have to repeat the extensive tests meant to prove drug efficacy and safety.

Many regulatory agencies also provide shorter windows of market exclusivity to drugs that meet certain qualifications. For example, a human or animal drug product that has not been previously approved (i.e., for other species or indications) is eligible for five years of market exclusivity from the FDA. During this period, which starts when the drug is approved, the FDA will not accept applications for generic versions of the drug. Because applications for generic drugs also take time to be approved, the effective period of market protection is longer than these five years.

### **3. A Simple Framework of Drug Development**

To clarify the factors that influence the drug development decision, we present a very simple framework of drug development that could be applied to either HP or AP and then discuss how relevant parameters differ between HP and AP. For this early discussion, we consider HP and AP R&D separate to characterize broadly factors that would differ between drug incentive programs in the two markets. Later we consider how linkages between the pharmaceutical sectors may impact how an incentive program in HP influences AP.

Firms choose among a large set of candidate research projects, each of which is described by development costs  $k_i$ , the probability of making it through the winnowing process  $p_i$ , and the value  $v_i$  of a marketable drug. We assume firms know at the outset all relevant parameters associated with a candidate drug. Let  $i$  denote the market where  $i = A$  denotes the AP market and  $i = H$  denotes the HP market. Firms are risk neutral and will develop a drug if the expected value of doing so exceeds an outside option, which we normalize to zero. That is, firms will choose to develop a drug if:

$$(1) \quad p_i v_i - k_i > 0$$

This framework allows us to neatly separate the factors affecting demand for a drug (which determines  $v_i$ ), the cost of registration and R&D (which determines  $k_i$ ), and the probability of making it to market (which determines  $p_i$ ).<sup>6</sup> When these parameters fully capture the (social) value, costs, and probability of success for a drug, then there is no need for the government to intervene in the market by providing additional incentives. However, if there are wedges between the social and private costs/benefits of a drug, then government intervention can improve welfare.

Various mechanisms have been proposed in drug incentive programs to increase  $v_H$ , lower  $k_H$ , and/or increase  $p_H$ . Each such policy will increase the net expected value of a candidate drug, which has the potential to push it from being a net negative to a net positive return proposition. The way these parameters are determined in HP and AP vary considerably,

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<sup>6</sup> This framework makes many simplifying assumptions. First, we have collapsed the multi-stage R&D process into one step, described by the single variable  $p_i$ , which now encapsulates the uncertainty that a drug will have therapeutic value, that it will pass safety and toxicological screens at the registration stage and so forth. Second, the value of a drug to a firm is not a given exogenous quantity, but the outcome of uncertain marketing and other post-R&D decisions. The variable  $v_i$  may be interpreted as the present-discounted expected value of the flow of revenues from a firm that is acting optimally to maximize its profits. Third, the costs of drug development are similarly spread over time, and uncertain. As with profit, we take  $k_i$  to be the present-discounted expected value of the flow of costs from a firm acting optimally.

and because of this incentive programs designed for HP may have greater or lesser impacts on AP.

The prior economic literature on spurring new drug development broadly divides the incentive mechanisms into “pull” and “push” levers; “pull” mechanisms increase the return to new drugs while “push” mechanisms lower the cost of R&D. Specific pull policies that have been suggested for HP include lump-sum prizes, patent extensions, patent purchase offers, drug sale price guarantees or supports, and quantity purchased guarantees (Williams, 2012; Kremer and Glennerster, 2004). Specific “push” mechanisms include funding foundational research, supporting open access to research, funding support during the development process, and providing refundable tax credits for research.

Many of these mechanisms have been grouped in already-adopted programs. For example, the 2012 Generating Antibiotics Incentives Now (GAIN) act increased the period of market exclusivity for qualified HP drugs and expedited the review of antibiotic drug applications. The Biometric Advanced Research and Development Authority (BARDA) has programs that pay contracted drug makers a fee for reaching certain milestones in the drug development process, and has subsidized R&D costs.

#### **4.1 Differences in the Market Values of Approved Animal versus Human Drugs**

“Pull” mechanisms in human pharma attempt to increase the returns to drug-makers by increasing  $v_H$ . We begin by examining how  $v_A$  and  $v_H$  differ.

##### *4.1.1 Human drugs have higher value*

As noted, the value of animal health drugs is much smaller than the value of human health drugs. One of the key reasons for this is simply that willingness to pay for food animal health is lower than the willingness to pay for human health. Farmers will not pay for drugs that make an animal

unprofitable to bring to market. This imposes a ceiling on the price of drugs that does not apply to human health. Low per-unit willingness to pay in the animal health market rules out the development of animal drugs that are very costly to manufacture and administer even if they are very effective, while the lower overall value of drugs in AP means a policy to raise  $v_i$  by a given percent will be less costly for animal health.

#### *4.1.2 Government intervention differs across markets*

Another difference between AP and HP is the extent of government intervention in the healthcare market. Programs like Medicare and Medicaid directly pay for a large share of human healthcare and provide a relatively direct (if blunt) instrument to the government if it wishes to raise the value of a given drug – it can simply pay more for it. Regulations to the human health insurance market provide a less direct way for the government to raise the value of a drug. For example, requiring insurers to provide coverage for certain classes of medical care may lead to more use of the care by patients. In contrast, there is no large government payer for animal healthcare, nor insurance for unexpected healthcare needs. While this does not preclude the possibility of the government providing price support to AP health products, it does mean that the mechanism through which these supports occur would differ.

#### *4.1.3 Patents are less important in animal pharma*

Another method of increasing the value of a drug is via patent and market exclusivity extensions. Patents can play an important role in the value of a marketed product. When a drug patent expires, rival firms may seek regulatory approval to begin manufacturing generic versions of the drug, eroding the market power and profits of the incumbent. However, this is less likely to occur in smaller markets when the cost of entry is similar.<sup>7</sup>

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<sup>7</sup> Suppose a patent confers monopoly value  $v_i$  and when the patent expires, a rival firm may pay  $k^g$  to enter the market as a generic competitor, at which point both firms earn  $\alpha v_i$ , where  $\alpha \in [0,0.5]$ . If  $k^g$  and  $\alpha$  are the same in

The relatively smaller size of the animal health market yields a relatively smaller (but not insignificant) role for patents. Drug profits are not as negatively impacted when a patent expires as in human health. For example, in its 2014 annual report, Eli Lilly noted:

Certain of our Elanco animal health products are covered by patents or other forms of intellectual property protection. Historically, upon loss of effective market exclusivity for our animal health products, we have not generally experienced the rapid and severe declines in revenues that are common in the human pharmaceutical segment. (Eli Lilly 2014, p. 8)

Moreover, Zoetis estimated in 2014 that 80 percent of its revenues were derived from products that either had no patent protection (patents were expired or never filed), or where patents provided incomplete market exclusivity (Zoetis 2014, p. 15). For comparison, patents are considered effective for appropriating market value for 50 percent of human pharmaceutical drugs (Cohen, Nelson, Walsh 2000). In contrast to the human pharmaceutical industry, there are no large, international, well-capitalized generic animal drug manufacturers. Generics account for just 10 percent of dispensed animal health drugs (PWC 2015).

In both human and animal medicine, many of the costs of entering the market with a generic drug are the same. To obtain regulatory approval, firms must establish bioequivalence and demonstrate the ability to manufacture the drug with best practices. In both cases, firms need to set up manufacturing facilities capable of producing large volumes with best practices. Indeed, in some ways, the animal market is more costly to enter. For example, if farmers are risk averse it may be difficult to induce them to switch to a generic drug, especially if price discounts are small (which they are likely to be, given the small margins in animal health). Moreover, to penetrate a market in human health, it may suffice to convince a small number of major insurers

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the human and animal markets, but  $v_A < v_H$  then there will be less entry by generic competitors in the animal health market when the patent expires.



that a generic product is equally good. In animal health, no such insurers exist, and firms instead need to reach out to the dispersed network of veterinarians who work with farmers (although in some markets, it might suffice to convince a small number of large animal producers). These factors suggest that patents extensions are a less effective method of influencing drug value in animal health than in human health.

## **4.2 Differences in the R&D Costs of Animal versus Human Drugs**

Drug incentive programs have also explored or adopted “push” mechanisms which attempt to lower the costs of R&D. In this section we examine how  $k_A$  and  $k_H$  differ.

### *4.2.1 Drug development costs higher in human pharma*

As noted in section 1, drug trial costs in human pharma are higher than in animal pharma. One reason for this is human clinical trials, which account for approximately 69 percent of out-of-pocket human drug costs (Dimasi, Grabowski, and Hansen 2016). Clinical trials for veterinary medicine are often much smaller (Palmer 2011) and may sometimes be skipped entirely if sufficient evidence of efficacy and safety is already available (Furdos et al. 2015). Moreover, when food animal drugs are tested on the target population, the tested animals can subsequently be sold on the market, further reducing the cost of drug trials (FDA 2015)<sup>8</sup>. The reduced costs of drug development mean a fixed budget can fund more AP drugs than HP drugs.

### *4.2.2 Multiple species and indications for drugs in animal pharma*

A second difference between HP and AP in R&D costs arises from the fact that animal drugs are often used in multiple species, while in HP there is only one. From our dataset on approved veterinary drugs in the US, 46% of non-generic veterinary drugs with a species listed on the label have a second species listed as well. Drug extension to multiple species -- as well as multiple

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<sup>8</sup> There are stringent measures in place to ensure drugs have been metabolized down to levels safe for human consumption before they enter the market.

label claims, dosages, and routes of administration -- is often necessary to generate positive returns for a drug, and is often done in steps. Regulatory approval may initially be sought for only a small number of high value species or indications. Later the drug sponsor will return to the regulator to seek market approval for additional species or extensions, requiring additional trials, but not necessarily the re-establishment of all facets of safety, efficacy and manufacturing best practices.<sup>9</sup> R&D conducted to extend the use of a drug to new species and therapeutic uses is part of what the industry calls “lifecycle management,” and accounts for a substantial fraction of R&D in AP. Note that new uses for an existing drug (such as new species or label claims) are not patentable discoveries, and it may be that lifecycle management takes place after patents have expired.

Lifecycle management can bias R&D away from innovative ideas for two reasons. Incumbents face a disincentive to invest in R&D to improve their products because in doing so they cannibalize the sale of their existing line of products (Arrow 1962). In HP, this problem is mitigated by competition from generics upon expiry of a patent: when a patent expires, incumbents lose the ability to profit off their existing products and therefore face a strong incentive to develop improved products. However, in AP, lifecycle management implies firms can continue to profit off the same product well after a patent expires. This can push firms to invest in incremental research that extends the use of existing products to new diseases and species, without undercutting the existing uses of a product, rather than radical breakthroughs that render existing products obsolete.

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<sup>9</sup> For example, Naxcel by Zoetis was granted its first approval to treat Bovine Respiratory Disease in cattle in 1988. The drug was extended to swine in 1992, equine in 1994, poultry in 1996, and goats in 2001 (PWC 2015). New formulations and claims were appended to the drug through 2009.

The long time horizon over which drug profits are realized in AP also presents a barrier to entry, as firms must be able to endure large up-front costs but may be compensated only over a very long time (longer than in HP). If innovative ideas come from entrants rather than incumbents, this can be a barrier to radical innovation. For these reasons, programs aimed at incentivizing radical innovation might need to target small entrants (for example, by providing liquidity) more than in HP.

The multiplicity of species involved in drugs adds an additional layer of complexity to the design of an incentive program. Which species are to be targeted? Can a drug designed for one species be “spun” out to additional ones? Should species be targeted all at once or sequentially? If species are to be targeted sequentially, this will increase the time required to fully realize a drug’s potential. In contrast to HP, where a “push” incentive program can stop when the drug reaches market, an AP push program may want to continue providing funding even after a drug has entered the market.

### **4.3 Incentives to Target the Probability of Success of Registration**

The literature on drug incentives does not generally discuss increasing the probability a drug will be cleared for marketing ( $p_i$ ), although doing so will also serve to increase the likelihood that developing the drug is cost-beneficial. There are two distinct ways a government could impact  $p_i$ . First, it could target the scientific uncertainty about whether a drug candidate “works” by supporting fundamental biological research.<sup>10</sup> This is distinct from directly funding registration testing costs ( $k_i$ ). “Fundamental” research would be aimed at significant scientific breakthroughs with the possibility of myriad eventual applications.

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<sup>10</sup> A greater understanding of the underlying biological sciences contributed to a shift in HP drug testing from “random” sampling of a wide array of molecules for therapeutic efficacy in the 1950s and 1960s to “rational” sampling of a subset of molecules, where the choice of molecule was guided by the scientific knowledge base (Scherer 2010).

Second, the government could adjust the standards a drug must meet to receive regulatory approval. For example, the FDA could require new drugs to be “safe,” or “safe and efficacious,” or “safe, efficacious, and better than the best current alternative.” The more requirements a drug must meet to receive approval, the lower is  $p_i$ . Some have also argued that when the FDA is assessing the statistical evidence of a drug’s efficacy, it should use different thresholds for statistical significance depending on the relative cost of Type I and Type II errors (Isakov, Lo, and Montazerhodjat 2015). Alternatively, drugs can be conditionally approved after meeting relatively low standards of evidence, subject to the requirement that more stringent standards are met later.<sup>11</sup> In this section, we discuss how  $p_A$  and  $p_H$  differ.

#### 4.3.1 Lower value relative to cost in AP means the probability of success needs to be higher

Recall we assumed a drug in either sector is developed if  $p_i v_i - k_i > 0$ . Let  $\bar{p}_i \equiv k_i/v_i$  be the minimum value of  $p_i$  that satisfies the above equation. The ratio of  $\bar{p}_A$  to  $\bar{p}_H$  tells us how much more certain the approval of an animal drug candidate must be relative to a human drug candidate for it to be worth pursuing. Substituting in the definitions of  $\bar{p}_i$ :

$$(2) \quad \bar{p}_A/\bar{p}_H = k_A/k_H \times v_H/v_A$$

Below, we estimate the R&D per new drug to be 4.7 times higher in HP than in AP. Using this as a benchmark,  $k_A/k_H \approx 1/4.7$ . To get a proxy for the relative value of a HP and AP drugs, recall that the HP market is approximately 50 times the size of the AP market. There are about 3.2 as many new molecular entities as there are AP drugs with an original ingredient, which implies every novel HP drug is worth, on average  $50/3.2 = 15.6$  times a novel AP drug. Alternatively, taking the anecdotal figure that blockbuster drugs in human health make \$1 billion per year

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<sup>11</sup> In 2004 the Minor Use and Minor Species Animal Health Act created a “conditional” drug approval program to encourage the development of drugs for minor species. Drugs for minor species can be conditionally approved based on demonstrating a drug’s safety, but not efficacy, for five years. During the five years of conditional approval, drugs sponsors can gather data from use of the drug.

versus \$100 million per year in animal health as broadly representative, an HP drug is worth 10 times an AP drug. Using these as rough estimates, then  $\frac{v_H}{v_A} \in [10,15.6]$  and  $\frac{\bar{p}_A}{\bar{p}_H} \in [2.1,3.4]$ . This crude calculation indicates animal drugs need to be two to three times as likely to pass registration as human drugs for it to be worth beginning registration.

The probability  $p_i$  can be interpreted as one measure of how fundamental and basic the research is. When a drug is more novel, there are more unknowns about its effects and likely side effects, which will reduce the probability it clears registration. These results imply drug companies will be less willing to take a chance on novel drugs in animal health, compared to human health. To induce equally novel drugs in AP and HP, incentive programs would need either to fund more fundamental research in AP so that there is less scientific uncertainty about novel AP drugs, or lower regulatory hurdles by a greater degree than for human pharma.

#### *4.3.2 AP market may require a weaker signal about drug efficacy than HP*

One of the functions of regulatory approval for drugs is to credibly signal to consumers that a drug is effective and safe. It is infeasible for most drug purchasers to independently verify drugs are effective and safe on their own to the same rigor as the regulator (it also wastefully duplicates effort). Drug trials require monitoring large groups of patients in order to detect small effects. Ideally the treated and untreated populations are identical, and assignment to treatment or the control group is perfectly enforced. This is impossible to achieve in human health, where patients are heterogeneous and largely make their own treatment decisions.

The same is not true for food animal production. A unique feature of this industry is the role of producers who sometimes oversee the management of a very large number of animals in a

relatively homogeneous setting.<sup>12</sup> Compared to human medical providers, animal producers have better opportunities to learn about the efficacy of medical interventions by observing the impact of interventions on the target population. They have the capacity to run their own experiments on large populations, which may allow them to bypass the regulator to some extent. More generally, whereas a human patient might experience a particular disease a few times in a life, animal producers may encounter it every year in at least some animals. If the same drugs are used each year, this provides greater information about their efficacy (as well as more incentive to determine efficacy). All of this suggests it may be possible to reduce oversight in AP relative to HP, and in so doing, increase  $p_A$  (and, incidentally, reduce  $k_A$ ).

## 5. Estimating the “Push” Costs of R&D Per New Animal Drug

Multiple strands of evidence indicate drug development for animal health costs a fraction of that in human health. Estimating the cost of drug development is a complex issue because costs are spread over many years and many candidate drugs, the majority of which are never approved. DiMasi, Grabowski and Hansen (2016), using firm survey data and taking into account spending on failed R&D projects, estimate the out-of-pocket cost of developing a human drug for the period 1995-2007 to be \$1.4 billion in 2013 dollars. No similar data for animal health exists, but in a survey of major pharmaceutical companies in 2011 by industry advocacy group HealthforAnimals the average cost of developing a new pharmaceutical product for food animals

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<sup>12</sup> For example, Tyson Foods owns and operates 63 broiler hatcheries (Tyson Foods 2016), and processed 35.4 million broilers *per week* (MacDonald 2014), all raised by contract growers under Tyson specifications. Cal-maine Foods, the country’s largest egg processor, has an inventory of 34 million layers in 44 production facilities (Cal-Maine Foods website, accessed May, 2017). Smithfield Foods, the country largest pork producer, had 880,000 sows in company and contract facilities in 2016 (Freese, 2016).

in the US was reported to be \$38.8 million (IFAH 2012), although estimates for individual drugs can run as high as \$100 million (Animal Health Institute 2012).<sup>13</sup>

We attempt to generate a comparable measure for HP and AP that takes into account measurement issues associated with sunk costs for compounds that do not reach the market by using industry-wide US R&D per new approved drug. This is displayed in Figure 2 for the period 1989-2007.

To provide a measure of the trend in R&D spent per new drug approved, we divide R&D spending by all firms by two measures of animal health product development 1) the total number of New Animal Drug Approvals (NADAs), and 2) the total number of NADAs with an original ingredient. We characterize an original ingredient as one that has not been approved previously (in combination or by itself). The first of these measures includes reformulations of ingredients, while the second provides a more precise measure of innovation. For all series we examine 9-year moving averages, due to the fluctuations in annual rates as well as the time lags between research spending and product approval. Fig. 3 shows that the dollars per new animal drug, whether measured as a NADA, or as a NADA with a new ingredient, are trending upwards, although at different rates. R&D dollars per NADA averaged \$32M in the period, while that figure was \$119M per NADA with an original ingredient (2009 real dollars). Fig. 3 represents an upper bound on R&D spending per new product, as we do not include biologics (combining pharmaceutical and biologic products in a single approval number is inappropriate due to different regulatory processes and scientific methods).

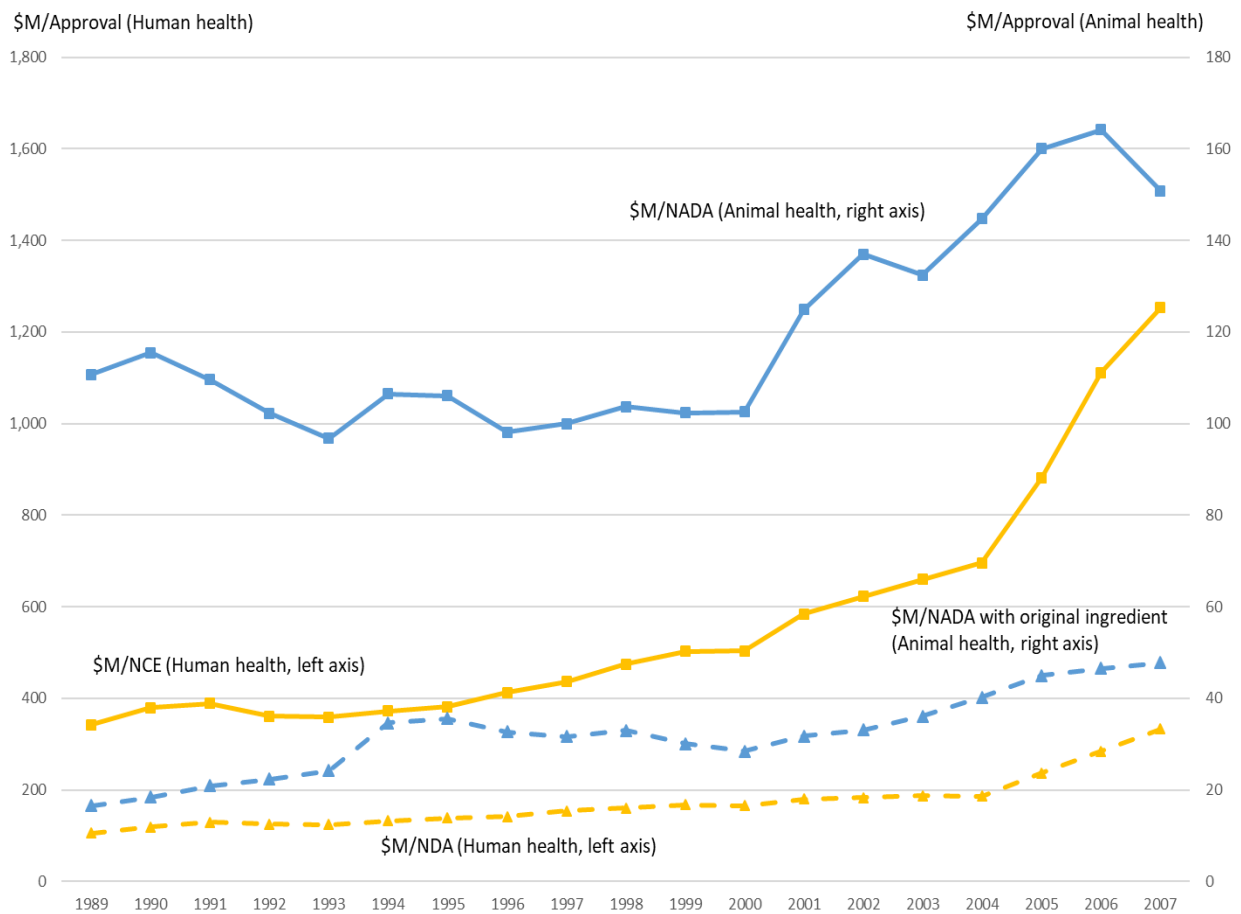
Fig. 3 also allows us to examine whether spending on animal human drugs is trending differently from human drugs; if they trend together, this suggests a driver that might be common

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<sup>13</sup> It is not clear if survey respondents are taking into account spending on failed drug programs, and they are likely not counting the cost of adding species and new claims to a drug after it has been discovered (IFAH 2012 estimates the cost of a new claim to be \$6.3 million in the USA).

to pharmaceutical development, rather than specifically for veterinary drugs. For human health we show two series, similar to those for animal health: 1) the R&D dollars per new drug approval (NDA), and 2) the R&D dollars per new chemical entity (NCE). Similarly to the animal health series, the first represents spending for all types of drugs, while the second more narrowly describes spending on innovative drugs. Note that research dollars spent on human pharmaceuticals are graphed on the left axis, which is 10 times higher than the animal pharmaceutical axis (on the right).

**Fig. 3. R&D spending per new drug, human versus animal health, 1989-2007, U.S.**



Sources: ERS calculations from FDA Green Books (animal NADAs), unpublished data from Fuglie (2016) (animal health R&D spending for the U.S.), NSF (2016; R&D spending on human health), and FDA (2013; number of new human drug approvals). See Appendix for more data description.



Notes: Calculated as centered nine-year moving average of real R&D divided by nine-year moving average of approvals, lagged five years. See Appendix for description of methodology. All values are in real 2009 dollars. NADA stands for New Animal Drug Approval. NDA stands for New Drug Approval. NCE stands for New Chemical Entity.

Comparing the human and animal R&D per product trends, we notice two things. First, the R&D spending in AP is a fraction of that in human health. In the period, the average amount spent per drug with a New Chemical Entity in the human health market was \$564M (2009 dollars), while that spent for any new human health drug was \$171M. In both instances, human health spending was approximately 5 times higher than in animal health. Second, the increase in the dollars spent per new pharmaceutical product is echoed in the human health market. The rise in the amount spent for the more innovative drugs shows a more marked increase in the period, compared to the measures showing spending for any type of drug.

In human health, the increase in R&D spending per drug is attributed to increased failure rates in drug testing and increased regulatory burdens (DiMasi, Grabowski, and Hansen, 2016). We do not have similar insight for the increase in animal health. What our findings do suggest is that an increasing R&D spending per new product in HP is correlated with a similar increase in AP.

## **6. Estimating the “Pull” to Bring a New Veterinary Drug to Market**

Our goal is to estimate the size of a “pull” mechanism that would incentivize the generation of an additional drug. To do this we make use of market sale for food animal products (meat and poultry) and the number of veterinary drug products approved for each category of food animal. This allows us to estimate an elasticity between market size and drug approvals, which we can then use to estimate the size of a “pull” incentive.

To estimate the elasticity of drug approvals to the size of the market, we run poisson regressions of the following type:

$$(2) \quad E[y_{st}] = \exp(\eta \log(\text{Own Market}_{st}) + X'\beta)$$

Where  $y_{st}$  is the number of drug approvals (non-generic or original) for species  $s$  in year  $t$ . We have market data on four major species: cattle, chickens, swine, and turkeys. We have observations for every year between 1962 (the first year drug sponsors needed to prove the efficacy of their products) and 2015.

We use estimates of commodity cash receipts, measured in real 2009 dollars, by the USDA Economic Research Service as our metric for the value of animal markets (Own Market). A potential problem with using species market value is the cross-species linkages of animal health. Many drugs are cross-listed for multiple species, and in other cases, the same underlying chemical elements are used to treat different species and diseases. It may be that a drug is not worth developing for the cattle or swine market alone, for example, but would be worth developing for the two together. Because the same drug may be applied to multiple species, we include total cash receipts across all of US animal agriculture (Total Market) as an additional control in some specifications.

In some specifications we include species and year fixed effects. We use a poisson fixed effects estimator to remove species fixed effects 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.

In any attempt to link market size with R&D one must decide which year's data is pertinent to the decision to begin R&D. Drug R&D is initiated many years before approval. If drug sponsors are rational and accurate forecasters, then they can anticipate the size of the market when a drug is approved. In this case, using the size of the market in the year a drug is approved is correct. If drug makers anticipate revenues flowing in the years after approval, then it may be appropriate to use the size of the market in years *after* approval. Conversely, if drug

makers are myopic and assume market size follows a random walk, then it is appropriate to use the market size in the years *before* approval. In the following tables, we make the first assumption, and use the size of the market in the same year a drug is approved. In unreported regressions, we verify this assumption does not drive our results. This is likely because lagged and leading market values are highly correlated with market value at the time of approval. As can be seen in figure 1, variation across species tends to be larger than variation within a species (indeed, we will find cross-species heterogeneity drives our results).

Tables 3 and 4 present our results. In Table 3, the dependent variable is the number of non-generic drugs (NADAs) per species-year. In Table 4, the dependent variable is the number of original drugs per species-year.

**Table 3. Market Size and Non-Generic Drug Approvals**

	Dependent variable: NADAs per year by species				
	(1)	(2)	(3)	(4)	(5)
Intercept	-5.17***	2.33	-5.82***		
	(1.157)	(9.211)	(0.777)		
log(Own Market)	0.39***	0.40***	0.41***	-0.09	0.43*
	(0.068)	(0.069)	(0.041)	(0.193)	(0.211)
log(Total Market)		-0.41		0.12	
		(0.498)		(0.330)	
Observations	216	216	216	216	216
Year Fixed Effects	N	N	Y	N	Y
Species Fixed Effects	N	N	N	Y	Y

**Table 4. Market Size and Original Drug Approvals**

	Dependent variable: Original drug approvals per year by species				
	(1)	(2)	(3)	(4)	(5)
Intercept	-8.04***	6.401	-8.46***		
	(2.003)	(15.668)	(1.578)		
log(Own Market)	0.46***	0.47***	0.47***	-1.32**	-1.23*
	(0.118)	(0.120)	(0.085)	(0.499)	(0.600)
log(Total Market)		-0.78		1.06	
		(0.848)		(0.827)	
Observations	216	216	216	216	216
Year Fixed Effects	N	N	Y	N	Y
Species Fixed Effects	N	N	N	Y	Y

For each table, column 1 includes only a constant and log(Own Market). For non-generic drug approvals, we find an elasticity of 0.4, a number that will prove fairly robust to alternative specifications. For original drugs, we find an elasticity of 0.5, a number that is less robust, and in particular appears to depend on cross-sectional variation. Column 2 adds log(Total Market) as an explanatory variable. This has little impact on the elasticity between drugs and the size of the species market. We cannot reject the null that the elasticity between the Total Market and drug approvals (non-generic or original) is zero. The elasticity of the “own market” rises slightly. Column 3 adds year fixed effects, but drops the log(Total Market) variable (which is unidentified, since it does not vary by species). This has no significant impact on the elasticity of the own market.

Column 4 introduces species fixed effects and retains the Total Market explanatory variable. This removes cross-species variation in the size of the market as a source of identification, and has substantial impacts on our estimated elasticities. In Table 1, we can no longer reject the null that the elasticity of demand is zero. In Table 2, the estimated elasticity switches signs and becomes substantially negative! Finally, in Column 5 we include year fixed

effects (and drop the Total Market variable). In Table 1, this suffices to restore the estimated elasticity to 0.4, as measured in specifications (1)-(3). In Table 2, the estimated elasticity remains negative and statistically distinguishable from zero.

Taken together, there is substantial *cross-sectional* evidence that the elasticity between drug development and the market is on the order of 0.4.-0.5: a 10% increase in the size of the market leads to a 4-5% increase the annual flow of health product approvals. This is in line with evidence on the elasticity of demand between market size and drugs for humans (see Dubois et al. 2015). The evidence for these elasticities when we include species fixed effects is considerably lower. The interpretation of these results is driven to a large extent by judgments about the importance of species-specific omitted variable bias, which we leave for future research.

## **7. Consequences of Connections between Human and Animal Pharma for Drug Incentive Programs**

The links between AP and HP mean a program to incentivize drug development in HP can have positive or negative spillovers on the supply of drugs available to AP. Structural features of the linkages between the industries can also create issues with product approval.

### *7.1. Human pharma subsidizes animal pharma R&D*

The human health sector may increase the supply of animal drugs via two channels. First, when a drug is first approved for HP, and then is considered for AP, AP can benefit from the information learned in HP registration. Basic testing may be applicable for both approval processes. Second, the human market will be more willing to fund exploratory discovery work that may, as a side-effect, generate new candidates that happen to be promising for the animal health market.

### *7.2 Human pharma taxing animal pharma R&D*

The existence of the human market, however, may also reduce the supply of drugs available to the animal health market. First, as in the case of antibiotics, usage of a drug in livestock may carry the risk of reducing the efficacy of the drug in humans. This leads to restrictions whereby certain drugs approved in HP cannot be approved in AP. Even without a current ban on a drug being approved for both markets, the risk of a future move may be enough that it lowers the expected value of approval in AP. It may also be that consumer knowledge that the drug is also sold to animals reduces willingness to pay by humans. It is also possible that the increase in drug discovery brought about by the existence of a human market is offset by the human market “keeping drugs to itself,” so that the animal health sector is worse off than it would be on its own.

### 7.3 *Firm specialization and transaction costs*

Firms will find it efficient to specialize in the domain for which they have low costs and to outsource other aspects of the drug development pipeline to firms with lower cost. In practice, while large drug manufacturers do conduct in house R&D, they outsource much of the discovery work to small biotech start-ups and universities, and our interviews suggest AP may be even more reliant on outsourcing the work of discovery than HP. Transactions between firms add costs to drug approval, decreasing whether or not it is worth carrying it through the approval process.

Transaction costs might be higher in animal health than in human health. Animal health firms acquire many molecules from external sources such as biotech startups. These startups may come from a variety of backgrounds such as private industry or university incubators, but their business model is typically premised – initially – on developing drugs for humans, which is often the only payoff large enough to justify the risks inherent in forming a startup. The fact that most

external sources of drugs are premised for the human market creates special problems for the animal health market. Information asymmetries abound. Startups developing novel drugs often do not know the scope of animal market demand, the unique regulatory processes required to obtain market approval, nor how to find reliable guides to the market.

Additional problems can emerge for drugs suitable in both markets. It may be that a startup firm has found two buyers for the drug, one in the human market and the other in the animal market. It is likely that the deal with the human market buyer is the more lucrative of the two, and if this buyer insists on exclusive rights to the drug, then the deal with the animal market may not happen.

Furthermore, there appear to be frictions even within health companies that operate in both the human and animal health space. As noted above, six of the top seven animal health firms are subsidiaries of general pharmaceutical companies. The animal health subsidiaries can and do obtain access to promising molecules developed by the human side of the firm. However, our interviews suggest this internal sharing is not a primary competitive advantage (indeed, the largest AP company by sales, Zoetis, split from its HP parent company in 2013). AP and HP may have separate research departments, even within the same company, and may not share information. Cultural frictions may also be important, with scientists working on human health viewing veterinary medicine as less prestigious.

#### *7.4. Discussion*

The interlinked nature of early-stage R&D in human and animal health markets creates some complex interactions. On the one hand, the existence of a large human market facilitates much more discovery research than the animal health sector could support on its own, but various

factors may also keep some of this increased discovery research from being adapted by the animal health industry.

AP's dependence on human drug discovery also leaves the animal health market vulnerable to changing research priorities in the human health arena. When human and animal health priorities overlap, discoveries in human health may be more easily applied to animal health, but when the two separate, it is difficult for animal health to conduct discovery research on its own to fill the void. Some trends suggest that human drug R&D is moving toward high mark-up, low volume personalized medicine (Miller, 2013). In this situation, there will be fewer cast-offs for AP that make economic sense. Policies that increase HP R&D might yield fewer results for AP than they have in the past.

This divergence may be particularly acute for antibiotics. The priority for HP is new classes of antibiotics that are effective against bacteria resistant to currently produced antibiotics. It is likely that any such class that is discovered would not be shared with AP, but rather kept in reserve. Meanwhile, HP may not be as interested in the kinds of "alternatives" to antibiotics that would be most useful in AP but which still require fundamental research and have few anticipated benefits for human medicine.

Factors or policies that increase the value of R&D may well operate over different timeframes for the animal health market. Policies targeting the AP space specifically are probably better suited to push AP firms into registering more drug candidates, but may do little to expand the set of drug candidates itself. Policies targeting the HP space specifically will do little to help AP in the short-run (and may even reduce the supply of drugs if HP firms keep more to themselves), but in the long-run it may expand the set of drug candidates available to AP and HP by increasing the amount of fundamental research.



## **8. Conclusions: Lessons from One Field to Another**

The main purpose of this article has been broadly to elucidate how proposed mechanisms for human pharmaceutical incentivization may be applied to the animal health sector. The production of new drugs in each market follows a broadly similar process: large R&D costs to filter out safe, effective, desirable drugs from a large pool of candidates and to get these drugs approved by the regulator. In many regards, economic work on the determinants of R&D – policy, industry structure, demand factors – is likely to apply similarly to the animal and human health markets. Indeed, we find the elasticity between market size and drug approvals falls in the range of estimates found in the human health literature (although we caution that these results are not robust to species fixed effects).

Significantly lower costs of research in AP suggest that incentive programs for new AP products could cost less than those for HP. Our estimates suggest that funding R&D for a new animal drug would cost one-fifth of that for a new human drug (\$119M for AP or \$564M for HP). However, AP is still heavily reliant on HP for fundamental research. Market demand and structure is such that the animal health market does not conduct as much basic, fundamental, or risky research. Furthermore, because the human market is so large and the underlying science is similar, policies that impact it may well spill over into the animal health market. Policies that enhance the value of R&D in human health will likely increase the supply of drug candidates for animal health, although possibly only after a long delay.

In animal health, consumers (livestock producers and veterinarians) may be more responsive to the price of drugs than in human health, as food animals generate market goods. Consumers also have greater scope and motivation to learn the value of drugs because they may treat many animals at one time and over time. This is related to a concept we did not address in

this paper, namely the differing market failures in HP and AP that might justify government intervention. The markets also differ significantly in the role of contagion spillovers, the use of insurance markets, and the size of the wedge between the social and private value of medical treatment. These factors may undercut the relevance of various interventions into the healthcare market that are designed to address these distortions, such as subsidies, medical innovation prizes, and the design of optimal insurance markets. On the other hand, given the small size of the market and the high costs of entry, issues of market power may be more relevant for AP, especially for drugs that are off-patent.

This paper is an initial foray into the economics of innovation in animal health and there is significant scope for further work. Policy discussion on incentivizing new veterinary health products is still relatively new, and policy-makers have yet to clarify the specific goals, funding, and scope of such programs. There are few interventions to study and assess. More broadly, the extent of data available in the AP space lags significantly that available in the HP space. Finally, the flow of knowledge need not be one-way. Because the industries shares a similar product development process, but varies in other institutional settings, studying AP may shed light on the impact of policy changes to the human health market, just as much as the study of HP sheds light on AP.

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