Applied Economic Perspectives and Policy (2019) volume 0, number 0, pp. 1–22.
doi:10.1093/aepp/ppz022

Submitted Article

Incentivizing New Veterinary Pharmaceutical Products to Combat Antibiotic Resistance

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Required disclaimer: The findings and conclusions in this presentation have not been formally disseminated by the US Department of Agriculture and should not be construed to represent any agency determination or policy. This research was supported by the US Department of Agriculture, Economic Research Service.
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Submitted 18 October 2018; editorial decision 7 May 2019.

Abstract *The development of alternative animal health products is one way to reduce antibiotic use in agriculture. However, little economic research is directed at animal pharma. While programs to incentivize research and development (R&D) for human drugs have been adopted, analogous programs in veterinary pharma are only at the proposal stage. 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 and firm-level R&D, we also present data on trends in drug development for veterinary pharma.*

Key words: Agriculture, Antibiotics, Innovation, Pharmaceutical markets, Incentives, Drugs, Animal pharma, Research and development.

JEL codes: L1, L65, O3, Q1.

Antibiotics are one of our most important tools for improving health, but their continued efficacy is not guaranteed. The US Centers for Disease Control and Prevention (CDC) estimate that over two million people in the United States become ill each year from antibiotic resistance infections, with at least 23,000 dying (US 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 (Outterson et al. 2013).

Antibiotics are widely used for 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; US CDC 2013). This negative externality presents a case for government intervention.[1] While scientific investigation of direct connections between on-farm antibiotic use and clinical human infections or the spread of resistant genes is ongoing, policy makers have adopted regulations to reduce agricultural antibiotic use as one method of combating resistance (Shryock and Richwine 2010; US FDA 2012, 2013).[2]

One shortcoming of relying on regulations is that restrictions on the choice 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 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 one alternative method of reducing agricultural antibiotic use, policymakers have begun to consider policies to incentivize the development of new health products by the animal pharmaceutical (AP) sector.[3,4] In September, 2017, the US Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) released a draft report calling for such a program (PACCARB 2017). While PACCARB's report focused on vaccines and better diagnostic tests, a host of possible new products are under exploration (Cheng et al. 2014).[5] These include bacteriophages, immunity modulating agents, prebiotics, probiotics, and innate defense molecules (see Cheng et al. 2014; Pew Charitable Trusts 2017). Many of these products

[1] *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.*

[2] *There are also policies to reduce the improper use of antibiotics in human health, but they are not the focus of this paper.*

[3] *We use the terms "animal pharmaceutical industry," "animal pharmaceutical sector," "animal pharma," and "veterinary pharma" as synonyms.*

[4] *Beyond regulations and pharma product incentive programs, other suggested policies to reduce antibiotic use in animal agriculture include user fees or taxes on antibiotics for agricultural use, more education and veterinary support to farmers, and subsidies for disease reduction farm management measures. Here we focus only on incentive programs. Comparing policies to see which is the most socially optimal would first require some parameterization of each of these policy's effects, as well estimates of the impacts of the policy. Basic parameterizations do not yet exist, thus this paper is an initial attempt to partially fill this gap.*

[5] *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 incentivizing new antibiotics that would be used in human* and *animal medicine. The literature on promoting R&D for new human-use antibiotics grapples with how to incentivize a drug that would rarely be used, as widespread use would lead to resistance and would decrease the drug's efficacy. This concern adds a layer of complexity that we are able to avoid in this paper.*

are still in exploratory stages and not yet on the market, a situation that an incentive program might alleviate.

Important questions remain about the costs of these potential products. Ideally they would raise farm productivity more than antibiotics, and would therefore be adopted based solely on private cost-benefit grounds. Increased productivity of these products means social planners would be less reliant on regulatory institutions to reduce antibiotic use in agriculture. However, in certain scenarios the products might also be desirable even if they do not increase productivity more than antibiotics. This would be the case when other features prevent use of antibiotics; these features include regulations, market demands for products raised with fewer antibiotics, and potential lack of availability of antibiotics.

Research and action on incentivizing new health products for human health is wide and deep (e.g., Kremer and Glennerster 2004; Sharma and Towse 2011; Outterson et al. 2015; Renwick, Brogan, and Mossialos 2016). However, analogous literature and programs for animal health products is nearly nonexistent—indeed, one of PACCARB's main recommendations was to establish an institute to study the issue.[6] This paper begins filling this research gap.

We begin by briefly describing our research methods and data. We next provide a description of the drug development and marketing process in AP, particularly in relation to human pharma (HP). We introduce a simple framework of research and development (R&D) for drugs, applicable to either human or animal pharma. The framework parameters delineate the "push" and "pull" mechanisms used to incentivize new drug development. In the next section we use our framework to discuss how market value, R&D costs, and probability of success differ across HP and AP. This provides an introductory assessment of the efficacy of employing HP incentive schemes in an AP context. In the course of this discussion we quantitatively estimate the cost of and trends in R&D per new human versus veterinary drug. We conclude with a discussion of questions in need of further research. Notably, the results of our data analysis are presented throughout the paper where appropriate, rather than in a single section.

Methods and Data

There is virtually no academic literature on the economics of the AP sector, let alone literature on incentivizing the industry to generate undersupplied goods deemed desirable for social welfare. Therefore, 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

We conducted thirty interviews with animal health industry stakeholders, academic researchers, and Federal regulators between late 2015 and early 2016. The goals of these interviews were to understand the contours, types of entities, processes, structures, and incentives of the industry.

[6]*The economics literature has largely not examined the industrial organization of the AP industry at all. Notable exceptions are Buhr, Holtkamp, and Sornsen (2011) and Fuglie et al. (2011).*

We initiated interviews through cold calls, peer contacts, or meetings at the 2015 National Institute for Animal Agriculture's Antibiotic Resistance Symposium. Half of the interviewees were members of the animal pharma industry, including representatives of major pharma companies, small start-up employees, and independent consultants. Another 10 interviews were with government researchers and regulators. Five interviews were with academics performing research on interventions to antibiotic use in agriculture.

Our method of selecting interviewees was not random and occurred largely through peer contacts. Therefore, we cannot suggest that the interviews provided us with an unbiased or complete picture of the AP industry. We therefore also relied on industry publications, consulting firm reports, and firm-level annual reports to confirm many of the concepts and industry features covered in interviews.

Interviews generally lasted one to three hours. To ensure confidentiality, we did not record these interviews or collect numeric data from interviewees. After our initial interviews we organized a public conference at which many of the interviewees spoke. These presentations serve as external documentation of many of the interviewees' statements.[7]

Data Collection

In addition to published statistics available through a variety of sources, we gathered our own data. First, to calculate the number of animal drug approvals per year, we developed a data set of US veterinary drug approvals from 1941 through 2017. Veterinary drug approvals are overseen by the FDA's Center for Veterinary Medicine (CVM). We text-scraped scanned images of Green Books, the annual listings of drug approvals published by CVM (US FDA various years). In each year after 1990, the annual Green Book provides a list of all new drugs approved in that year. The 1989 Green Book lists all approvals prior to 1989 and the year of approval. This gives us years of drug approvals, drug ingredients, and the unique drug identifier; the drug identifier is a six-digit number assigned to a New Animal Drug Application (NADA) for nongeneric drugs, and an Abbreviated New Animal Drug Application (ANADA) for generic drugs. When we have missing information, we supplement with web-scraping of the FDA's website listing of all animal drug approvals (Animal Drugs @ FDA).[8] We also use published listings of monthly drug approvals from the FDA-CVM website for 2016 and 2017. For this manuscript we largely utilize data from 1985 to 2017, although we need the data for all drugs ever approved in order to characterize which drugs have never-before-approved "original" ingredients.

Second, we access data on all approved new drug applications (NDAs) for humans from the FDA's website. This allows a user to download all products (for human use) ever approved by the FDA's Center for Drug Evaluation and Research (CDER). From this we characterize year of approval, generic status, and whether the product is a "new molecular entity"

[7]*The presentations can be found at https://www.farmfoundation.org/projects/incentives-disincentives-for-research-development-of-new-antimicrobial-drugs-alternatives-to-antibiotics-for-food-animals-1925-d1/. (accessed August 13, 2019).*

[8]*Unlike the Green Books, the website does not list drugs that have been withdrawn and does not list the year of approval. Hence we could not use it as our primary data source.*

(NME); a "new molecular entity" is a product that contains "active moieties that have not been approved by FDA previously" (US FDA 2018). We use data from 1985 to 2017.

Third, we use updated data on veterinary pharma R&D spending originally published in Fuglie et al. (2011). As noted in Fuglie et al. (2011), R&D spending is "estimated from company financial reports and as reported in Animal Pharm Reports" (86). Animal Pharm is an industry group that collects data from the major firms. We use the series from 1980 to 2017. Fuglie has updated this data to 2017 and provided us with the series via personal communication.

Fourth, we utilize a series of human pharma R&D spending from the industry group Pharmaceutical Research and Manufacturers of America (PhRMA). We utilize 2018 and 2013 annual industry profile reports from PhRMA to construct reported R&D spending for 1980 to 2017.[9]

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 be similar to one in HP. Both industries are R&D intensive; in 2015 the ratio of R&D to sales was 8–8.9% in AP (HealthforAnimals 2015) and 19.7% in HP (PhRMA 2018). For comparison, R&D's share of GDP was 2.7% in 2015 (National Science Foundation 2018). Both industries' R&D relies on similar techniques to develop similar drugs to treat related (but not identical) illnesses. 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 in 2017 four of the top six largest companies selling animal drugs were divisions of HP companies (table 1). The leading AP company Zoetis was itself a division of the HP company Pfizer until it was spun off in 2013. Together, these six companies accounted for 62% of sales in the animal health market in 2017.

While AP is a large global presence, it is small in comparison to HP. In 2016, HP realized over one trillion dollars in global sales (QuintilesIMS Institute 2016), thirty-five times that of AP sales in the same year ($32 billion) (HealthforAnimals 2018). 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).

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. This phase includes fundamental research, which attempts to explain the mechanisms of observed phenomena, as well as research that to

[9]*Notably, there is a separate series published by the National Science Foundation (NSF) for pharma R&D, and the PhRMA and NSF series diverge in about 1984 (US CBO 2006). The NSF series excludes R&D spending on trials that are performed post-market as well as development of manufacturing processes. The NSF series also excludes firms that sell their own products "if sales activities account for the largest share of payroll" (CBO 2006, 7). We chose to use the PhRMA numbers for spending on human R&D because of their greater similarity to the R&D spending captured by the animal pharma series from Fuglie.*

Table 1 Major Animal Health Companies' Sales, 2017

Parent Company	Animal Health Divisions	Total Revenue (M$)	Animal Health Revenue (M$)	Share of Parent Total Revenue in Animal Health (%)
Zoetis	. . .	4,888	4,888	100%
Boehringer-Ingelheim	Boehringher-Ingelheim Animal Health	20,036	4,408	22%
Merck	Merck Animal Health	40,122	3,875	10%
Eli Lilly and Company	Elanco	22,871	3,086	13%
IDEXX Laboratories	. . .	1,832	1,832	100%
Bayer	Bayer Animal Health	38,253	1,775	5%
CEVA	. . .	1,243	1,243	100%
Virbac	. . .	974	974	100%
Phibro	. . .	764	764	100%
Dechra Pharmaceuticals	. . .	456	456	100%

Sources: Animal Pharm (2017), Boehringer-Ingelheim (2017), Merck (2017), Bayer (2017), Eli Lilly (2017).

determine whether a compound meets a set of desirable criteria. 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 pass discovery proceed to the second stage of the drug development pathway: registration. This stage entails extensive testing 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 United States, nonbiologic 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 (i.e., a non-human animal) but also for the human consumers of the food product, as well as safe for the environment.

Compounds that are found to be effective for human use are typically prioritized for that market because it is much larger, and so animal health companies often work with compounds that have undesirable properties for humans. If human and animal pharma are within the same parent company, this makes such research sharing easier. However, human and animal pharma may have separate research departments, even within the same company, and may not share information.

This testing is costly and time-consuming. Approvals for innovative human drugs may take up to twelve years (US CBO 2006), while approvals for new animal drug approvals reportedly take 7 to 10 years (Animal Health Institute 2012). After many years of incurring costs, a successful product may be marketed and begin to make a return. However, for the initial time period after a product is released, sales are merely recouping R&D costs. It may take over a decade after approval before the product fully recovers R&D costs.

Due to the relatively smaller size of the AP market and high costs for approvals, the number of approved animal drug products is smaller than that for human health. Figure 2 displays centered 9-year moving averages[10] for the following series: (1) the number of approved new drug applications (NDAs) for humans; (2) the number of approved new animal drug applications (NADAs); (3) the number of NDAs with a new molecular entity; and (4) the number of NADAs with an original ingredient. The first of these two series are comparable for human versus veterinary nongeneric drug approvals.[11] The third and fourth series provide sharper measures of drug innovation. In the relevant literature, NDAs with a new molecular entity serve as indications of innovation. The term "new molecular entity" is assigned by the FDA's approval body. For animal drugs, no similar distinction for innovative drugs is made by the approving body. We therefore characterize animal drug approvals as "original" when they contain a chemical ingredient that has never been approved by itself or in combination with other ingredients.

Note that the scale for the number of drug approvals for animals is a quarter of that for humans; between 1989 and 2017, HP carried 7.0 times the number of new non-generic drugs through the approval pipeline as AP (3,056 vs. 437). HP also had 6.4 times the number of innovative drugs as AP (799 vs. 124).

The number of nongeneric human drug approvals remained fairly constant in the time period, while the number of nongeneric animal drug approvals declined. However, the two measures of greater innovation also appear to remain fairly steady over the period. This may be indicative of a lessening in the applicability of human drugs for animals.

After approval, HP and AP also adopt similar methods to protect their intellectual property. Both HP and AP make extensive use of patents (Arora, Ceccagnoli, and Cohen 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

[10] *We show the nine-year moving averages because the number of products generated greatly fluctuates from year-to-year. Let N_t be drug approvals in year t. The centered nine-year moving average is calculated as: $\bar{N}_t = \left(\frac{1}{9}\right)(N_t + \sum_{i=1}^{4}(N_{t-i} + N_{t+i}))$.*

[11] *We restrict our analysis to nongeneric drugs, as we later examine R&D spending per new drug approval. Very little R&D is devoted to generic approval, by design.*

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.

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. 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:

$$p_i v_i - k_i > 0 \tag{1}$$

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).[12] 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, potentially pushing it from being a net negative to a net positive return proposition. The way these parameters are determined in HP and AP vary considerably, so incentive programs designed for HP may have greater or lesser impacts on AP.

[12]*This framework makes many simplifying assumptions. First, we have collapsed the multistage 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.*

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 (Kremer and Glennerster 2004; Williams 2012). 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 bundled together 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.

Differences in the Market Values of Approved Animal versus Human Drugs

"Pull" mechanisms attempt to increase the returns to drug-makers by increasing v_i.

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. 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.

Government Intervention Differs across Markets

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 over the human health insurance market provide a less direct way for the government to raise the value of a drug. In contrast, there is no large government payer for animal healthcare. 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.

Patents 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. Expedited approval of generic versions of off-patent drugs has been available in the United States since 1984 for human health (Branstetter, Chatterjee, and Higgins 2014) and since 1989 for animal health (Clancy and Sneeringer 2018). The importance of patents in animal health, relative to their importance in human health, is ambiguous.

There are some indications that AP 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, 8)

Moreover, Zoetis estimated in 2014 that 80% 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, 15). For comparison, patents are considered effective for appropriating market value for 50% of human pharmaceutical drugs (Cohen, Nelson, and Walsh 2000).

Generics also account for a smaller share of the AP market than the HP market. In 2004, generic drugs accounted for 45% of global animal health product sales (Gerecke 2004), compared to 89% of dispensed human prescriptions (Association for Accessible Medicines 2017). Moreover, between 1989 and 2017, 76% of the human drugs approved were generics, while only 45% of animal drugs were (authors' calculations from FDA data).

But other evidence does suggest generic competition is a substantial drag on AP profits, and therefore that patents play a major role in drug value. Clancy and Sneeringer (2018) find AP companies substantially reduce investment in original R&D in sectors facing more generic competition. Moreover, a 2004 report by Animal Pharm on the generic drug sector (Gerecke 2004) highlighted mounting concerns over generic competition.

From a theoretical perspective, it is not clear how important patents should be in AP, relative to HP. For example, because the value of AP drugs is small relative to HP drugs, it may be that markets are too small to support generic entry if the cost of entry is similar in AP and HP, with or without patents.[13] This would tend to make patents less important in AP. Conversely, the absence of third-party health insurers may make farmers more price sensitive to generics than in HP. Large producers may be

[13] *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 αv_i, where $\alpha \in [0, 0.5]$. If k^g and α are the same in 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.*

sensitive to even small changes in per-unit costs of drugs. This would tend to make generic competition, and therefore patents, more important in AP than in HP.

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 (k_i).

Drug Development Costs Higher in Human Pharma

As noted above, 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% 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 (Fürdös 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 (US FDA 2015).[14] The reduced costs of drug development mean a fixed budget can fund more AP drugs than HP drugs.

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 collected through convenience samples 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 $1.5B (updated from 2013 dollars to 2017 dollars using the Bureau of Economic Analysis's Biomedical Research and Development Price Index – BRDPI). A review of studies of human pharma R&D spending per drug shows a range between $82 M and $1.1B (Morgan et al. 2010; updated from the published 2009 numbers to 2017 USD using the BRDPI).

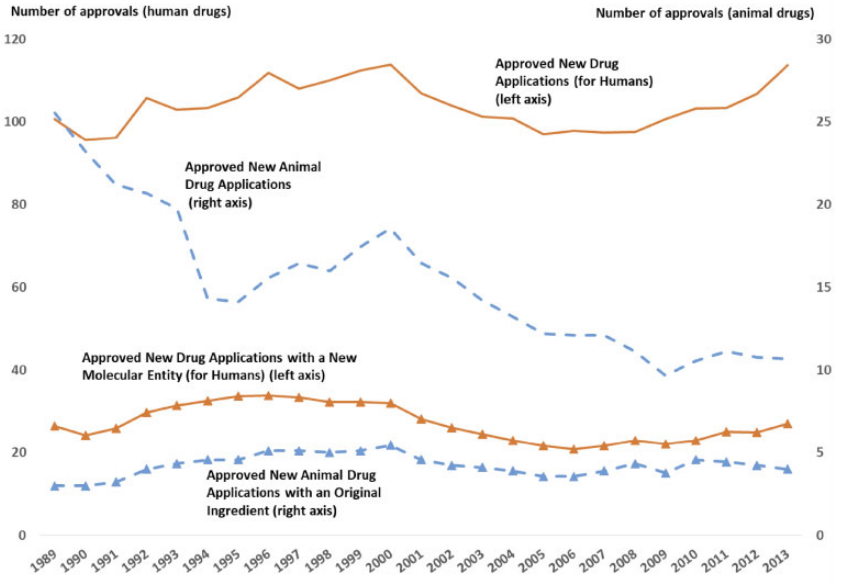
No similar data for animal health exists, but in a survey of major pharmaceutical companies in 2011 by industry advocacy group HealthforAnimals the average cost of developing a new pharmaceutical product for food animals in the United States was reported to be $43.7 million (IFAH 2012; updated from 2011 dollars to 2017 dollars using the BRDPI). Estimates for individual drugs can run as high as $113 million (Animal Health Institute 2012; updated from 2011 dollars to 2017 dollars using the BRDPI). It is not clear if survey respondents are taking into account spending on failed drug programs or counting the cost of adding species and new claims to a drug after it has been approved (IFAH 2012 estimates the cost of a new claim to be $6.3 million in the USA).

We attempt to generate a comparable measure for HP and AP for R&D costs per drug approval 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 1989–2013.

[14] *There are stringent measures in place to ensure drugs have been metabolized down to levels safe for human consumption before they enter the market.*

Figure 1 Number of new nongeneric human versus animal drug approvals, 1989–2013, centered nine-year moving averages

Source: Calculations from FDA CDR and FDA CVM data. A nine-year-moving average is estimated by averaging the values for four year prior to the year in question, the four years after the year in question, and the year in question. Because our data ends in 2017, we can only calculate the nine-year moving average to 2013.



To provide a measure of the trend in R&D spent per new drug approved, we divide total R&D for animal and human pharma spending by two measures of health product development. These are the measures shown in figure 1 and show either R&D dollars per (1) approved non-generic drug application (in animal or human pharma) or (2) approved nongeneric drug application with an innovative ingredient (in animal or human pharma). "Innovative ingredients" refers to either a new molecular entity (NME) in human pharma or a drug with an original ingredient in animal pharma. For all series we examine lagged nine-year moving averages; we lag R&D spending by 5 years due to the lag between research spending and product approval.[15]

Figure 2 shows that the dollars per new drug are increasing for all series, although at different rates. Notice that the left axis showing R&D spending per human drug approval is ten times the right axis showing R&D spending per animal drug approval. Figure 2 represents an upper bound on R&D spending per new product, as we do not include biologics like vaccines (combining pharmaceutical and biologic products in a single approval number is inappropriate due to different regulatory processes and scientific methods).

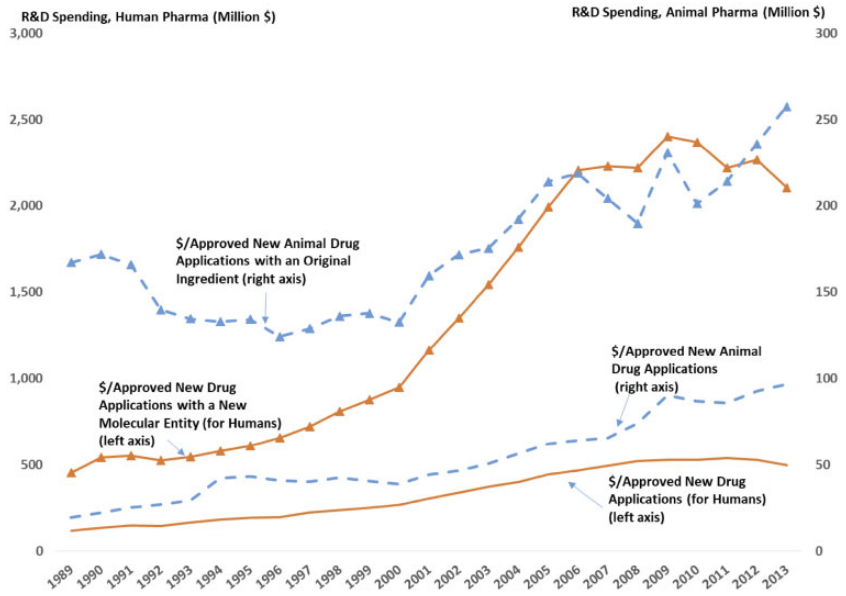
Comparing the human and animal R&D per product trends, we notice two things. First, the R&D spending in AP is a fraction of that in human

[15]*Let R_t be R&D spending year t. The centered nine-year moving average is calculated as $\bar{R}_t = \left(\frac{1}{9}\right)(R_t + \sum_{i=1}^{4}(R_{t-i} + R_{t+i}))$. $\bar{N}_t$ is the nine-year moving average of drug approvals centered in year t. Lagged spending per drug is therefore: $S_t = \bar{R}_{t-5}/\bar{N}_t$.*

Figure 2 R&D spending per new drug approval, human versus animal health, 1989–2013, Lagged and centered nine-year moving averages

Sources: Calculations from FDA Green Books (animal NADAs), unpublished data from Fuglie (animal health R&D spending for the US), PhRMA (2013, 2018; R&D spending on human health), and FDA CDER (number of new human drug approvals).

Note: Calculated as centered nine-year moving average of real R&D divided by nine-year moving average of approvals, lagged five years. Converted from nominal dollars to 2017 real USD using the Bureau of Economic Analysis's Biomedical Research and Development Price Index (BRDPI).



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.

Table 2 summarizes the approval and R&D numbers. Human pharma spends nearly fifty times that of animal pharma in total R&D and generates 8.2 times as many non-generic drugs, and 6.6 times as many innovative drugs. This results in human drug R&D being 4.8 to 6.2 times as expensive as animal drug R&D, per approved drug.

As noted above, candidate molecules are often originally studied for human drugs and then considered for animal applications. This overlap in fundamental research and some testing means that HP may subsidize AP R&D. Therefore our estimates for the difference in R&D costs for human versus animal drugs may be lower. Some portion of human drug R&D may be utilized in generating AP drugs, such that spending per new human drug is lower, while that for animal drugs is higher. We do not have a sense of what

Table 2 Approved Drug Applications and R&D Spending, 1985–2017, Animal versus Human Pharma

	Human	Animal	Ratio
Average annual R&D spending for all firms (1985–2012) (Million $)	38,301	785	48.8
Average drug approvals per year (1990–2017)	105	13	8.2
Average drug approvals per year with innovative ingredient (1990–2017)	28	4	6.6
Average Lagged R&D / Approval (1990– 2012) (Million $)	372	77	4.8
Average Lagged R&D / Approval with Innovative Ingredient (1990–2012) (Million $)	1,582	257	6.2

Sources: Calculations from FDA data, PhRMA statistics, and Fuglie data. All dollar values are in real 2017 dollars. The time period 1985 to 2012 is shown for R&D, as the R&D per new drug approval estimates are lagged.

percentage of molecules originally considered for human drugs eventually are utilized in animal pharma, hence we are unable to estimate how much the difference in R&D for HP versus AP might be reduced.

However, the existence of the human pharma market may also reduce the supply of drugs available to the animal health market. For example, usage of a drug in livestock may carry the risk of reducing the efficacy of the drug in humans, as in the case of antibiotics. 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 (from HP to AP) may be enough that it lowers the expected value of approval in AP.[16] In this way, R&D used for HP may not be applicable to AP.

Furthermore, there appear to be frictions even within health companies that operate in both the human and animal health space. As noted above, four of the top six 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. 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.

Multiple Species and Indications for Drugs in Animal Pharma

Another 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 species. From our dataset on approved veterinary drugs in the United States, 46% of nongeneric veterinary drugs with a species listed on

[16]*For example, fluoroquinolones were approved for human uses in 1986, and then were approved for use in poultry production in beginning in 1995. Multiple studies from the late-1990s showed increasing prevalence of fluoroquinolone resistance. After a lengthy review process, FDA withdrew approval of fluoroquinolones for use in poultry production in 2005 (Nelson et al. 2007).*

the label have a second species listed as well. Drug extension to multiple species—as well as multiple 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.[17] 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 (HealthforAnimals 2015). 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.

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). It may be harder for entrants to raise funding, given the lower level of assets to pledge as collateral. 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 (e.g., by providing liquidity) more than in HP.

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. While large drug manufacturers do conduct in-house R&D, they outsource much of the discovery work to small biotech start-ups and universities. Transactions between firms add costs to drug approval, decreasing whether or not it is worth carrying it through the approval process.

Relative transaction costs might be higher in animal health than in human health due to search and matching frictions. Like human pharma firms, animal health firms acquire many molecules from external sources such as biotech startups. These startups come from a variety of backgrounds such as

[17] *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.*

private industry or university incubators, but their business model is typically targeted on the larger human pharma market. This creates special problems for the animal health market. 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.

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 influence p_i. First, it could target the scientific uncertainty about whether a drug candidate "works" by supporting fundamental biological research. 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.

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 the disease (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.[18] In this section, we discuss how p_A and p_H differ.

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 $\bar{p}_i$:

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

Above, we estimated the R&D per new drug to be 4.8 times higher in HP than in AP. Using this as a benchmark, $\frac{k_A}{k_H} = \frac{1}{4.8}$. To get a proxy for the relative value of a HP and AP drugs, recall from above that a "blockbuster" human drug made 10 times as much as a "blockbuster" animal drug. Thus, we

[18] *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. Presumably, policies to increase the likelihood of regulatory approval would relax efficacy but not safety standards.*

can use $\frac{v_H}{v_A} = 10$. Using these as rough estimates, then $\frac{\bar{p}_A}{\bar{p}_H} \approx 2.1$. This crude calculation indicates an animal drug needs to be over twice as likely to pass registration as a human drug 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.

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. Most drug purchasers cannot feasibly and independently verify drugs as 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.[19] 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 lower regulatory stringency in AP, relative to HP, may be appropriate. This would also serve to increase p_A (and, incidentally, reduce k_A).

Conclusions: Lessons from One Field to Another

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 about one-fifth of that for a new human drug. However, AP is still heavily reliant on HP for fundamental research. Market demand and structure is such that the animal

[19] *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 36 million layers in 42 production facilities (Cal-Maine Foods 2018). Smithfield Foods, the country largest pork producer, had 880,000 sows in company and contract facilities in 2016 (Freese 2016).*

health market does not conduct as much basic, fundamental, or risky research. 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. These factors suggest that a program to incentivize new human drugs may have benefits for the AP sector.

AP's dependence on human drug discovery also leaves the animal health market vulnerable to changing research priorities in the human health arena. 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. Various factors may also keep some of this increased discovery research from being adapted by the animal health industry.

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. These factors suggest that a separate program for new pharma products might need to be aimed at AP.

Finally, the flow of knowledge need not be one-way. Because the industries shares a similar product development process, but vary 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.

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. Important questions remain on which products to incentivize, the characteristics of those products, and how to encourage adoption of new products (even if they are cost-beneficial).

Research on incentivizing development of new human drugs has also explored specific programs, such as prizes, funding aimed at specific research phases, and changes in drug approval processes. We have described how the broad levers of the costs of drug development (returns at market, costs of research and registration, and probability of approval success) differ between the human and animal pharma markets. Further research is necessary to examine which specific programs (or combinations of programs) might be more or less beneficial in the animal market.

To support this research, more data collection and availability needs to occur for the animal pharma market. Data availability in the AP space lags significantly that in the HP space. To understand linkages between drug molecule transfers from the human to animal markets, we need to simultaneously assess drug ingredients in both markets. Estimates for R&D costs by type of pharma product may be better estimated by assigning approvals to individual firms and tracking these approvals through market consolidation.

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