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The U.S. and EU Animal Pharmaceutical Industries in the Age of Antibiotic Resistance

Stacy Sneeringer, Maria Bowman, and Matthew Clancy





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Abstract

The animal pharmaceutical industry (or “animal pharma”) develops and sells antibiotic drugs and other products used for food and companion animals. However, the use of antibiotics in agriculture is under increasing scrutiny from policymakers and consumers. How animal pharma responds in terms of developing and marketing veterinary products has ramifications for agricultural production and meat prices. This report analyzes trends in sales and development of veterinary antibiotics. Antibiotics sales for food-animal production in the United States and the European Union (EU) have shown declines, even as demand for food-animal products continues to increase. The number of veterinary drug and biological products brought through regulatory approval in the United States also declined between 1989 and 2015, and antibiotics for food-animal production account for a decreasing share of new drug approvals.

Keywords: Antibiotics, veterinary pharmaceuticals, vaccines, livestock, economics, animal pharmaceuticals, innovation, drugs

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What Is the Issue?

Antibiotic drugs are a lifesaving technology widely used in human and veterinary medicine. However, the use of antibiotic drugs also creates selective evolutionary pressures that can spawn microbes and genes resistant to the drugs. Antimicrobial resistance has become an important global human health concern, with widespread public and private initiatives aimed at managing resistance.

The animal pharmaceutical industry (or “animal pharma”), a research-intensive business, is the source of antimicrobial drugs, biological products (like vaccines), pharmaceuticals other than antibiotics, and other health products for animals. It develops and markets products not only for livestock but also for companion animals like dogs and cats.

Animal pharma has been pivotal in driving agricultural productivity growth worldwide. However, the industry faces new challenges with the growth of concern over antimicrobial resistance. The demand for animal pharma products, the development of new products, and the regulatory environment are all affected by antimicrobial resistance concerns.

On the one hand, growing concern has led to more rigorous regulations on the use of antibiotics in food-animal production, rising demand for food products raised without antibiotics, and wider adoption of disease-reduction methods. These developments, in turn, may have the effect of decreasing sales of antibiotic products, lowering incentives to invest in new livestock antibiotics, and raising incentives to invest in non-antibiotic products. On the other hand, growing export demand for meat from the United States and the European Union (EU), rising animal disease pressures brought about by increasing globalization, and antibiotic resistance in animals may accelerate demand for antibiotics use and continue to provide incentives to develop new veterinary antibiotics.

Integrating data from many sources, this report analyzes the trends in sales of veterinary antibiotics and new product development by the U.S. and EU animal pharma industries. U.S. and EU regulatory processes are the focus because the United States and EU comprise approximately 60 percent of the animal pharma market and host the headquarters of all of the leading animal pharma firms. Furthermore, because many products are initially aimed at U.S. and EU markets, they are generally subject to approval through U.S. or EU regulatory processes.

ERS is a primary source of economic research and analysis from the U.S. Department of Agriculture, providing timely information on economic and policy issues related to agriculture, food, the environment, and rural America.

What Did the Study Find?

Sales of Antibiotics for Food-Animal Production

Between 2015 and 2017, total U.S. sales of antibiotics for food-animal production declined 30 percent (by weight), after annual increases in each year between 2009 and 2015. From 2010 to 2015, in 17 EU countries, antibiotics sales for production dropped 31 percent. The following factors have influenced these sales:

- U.S. consumer demand for products raised without any antibiotics has risen, particularly for poultry. In 2017, approximately 44 percent of U.S. broilers were raised without antibiotics, up from 2.7 percent in 2012.
- The steady increase in U.S. and EU production of meat over the past two decades—largely due to rising export demand, particularly from Asia—is raising demand for antibiotics sales in the United States and EU.
- U.S. restrictions on use of growth-promoting antibiotics enacted in 2017 appear to have contributed to declines in antibiotics sales, and similar European regulations are generally correlated with declines in overall antibiotics sales.

Development and Approval of New Animal Pharmaceutical Products

- Although research and development (R&D) dollars spent in the animal pharma industry have increased, the number of new animal drugs approved in the United States has declined, leading to an increase in R&D dollars spent per newly approved drug.
- Besides declining in number, new drug approvals have also changed in type: companion-animal products constitute an increasing share of new animal drug approvals in the United States. Because most drugs are not approved for both food and companion-animal use, this finding suggests the increasing share of animal pharma R&D devoted to companion-animal pharmaceuticals comes at the expense of food-animal pharmaceuticals.
- Approvals of food-animal antibiotics have declined both in number and as a share of approvals of all food-animal pharmaceuticals. Since 1992, most new antibiotic approvals for use in food animals have been generic drugs that are also used in human medicine.
- Since the inception of generic drugs in the United States in 1992, these drugs account for approximately half of new U.S.-approved veterinary drugs. Drug categories with the most generic competition also tend to have fewer drugs with novel active ingredients, suggesting that generic competition may tend to suppress R&D in these categories.
- A 2003 regulation increasing requirements for new antibiotics approved for food-animal use did not affect the number or types of antibiotics brought through regulatory approval.

How Was the Study Conducted?

This report compiles and analyzes data from a variety of sources, including meat production and export data from multiple countries, antibiotics sales data from both the U.S. Food and Drug Administration's Center for Veterinary Medicine and the European Medicines Agency, animal pharmaceutical industry data from firm annual reports and industry trade groups, and license data for U.S. veterinary biologics from USDA's Center for Veterinary Biologics. Trends in antibiotics sales and development for food-animal use are analyzed using a newly generated dataset of animal pharmaceutical product approvals. An econometric model is used to analyze whether drug development was affected by the introduction of a 2003 regulation requiring more robust testing for approval of new food-animal antibiotics.

The U.S. and EU Animal Pharmaceutical Industries in the Age of Antibiotic Resistance

Introduction

Antibiotics are a lifesaving technology widely used in human and veterinary medicine. However, the use of antibiotic drugs—by humans or animals—also creates selective evolutionary pressures that can spawn microbes and genes resistant to the drugs. Antimicrobial resistance has become an important global human health concern, with widespread public and private initiatives aimed at managing resistance. Livestock agriculture is a major consumer of antibiotics and contributes to antibiotic resistance. As such, it is a focus of policymaking and consumer advocacy surrounding antibiotics use.

As the agricultural use of antibiotics has become a greater policy and consumer focus, the animal pharmaceutical industry—the developers and marketers of antibiotics for food animal¹ use—have recalculated potential revenues from antibiotic products as well as investment into new products (e.g., PWC (2015)). By developing and marketing antibiotics and other products that affect animal welfare, performance, and disease, the animal pharmaceutical industry (or “animal pharma”) plays a pivotal role in domestic and international agricultural productivity—similar to the impacts of the biotech, seed, and pesticide industries. Animal pharma’s future product sales and development have important ramifications for agriculture, and by extension, consumers. Regulatory and market forces on antibiotics sales will both shape and be affected by the products animal pharma invests in.

Additionally, animal pharma research and production decisions will affect the future course of antimicrobial resistance, animal health options, agricultural productivity growth, and private initiatives on antimicrobial resistance. Therefore, it’s important to understand animal pharma’s organization and incentives to initiate and evaluate strategies aimed at influencing antimicrobial resistance. Until this report, an integrated top-to-bottom analysis of where antibiotics come from, where they go, and what factors drive these questions did not exist. This report begins to fill that gap.

In high-income regions like the United States and the European Union (EU), regulations restricting certain uses of antibiotics in agriculture, production-level management practices yielding fewer disease pressures, and consumer demands for food products raised without any antibiotics may lessen demand for antibiotics. If antibiotics demand declines, the animal pharma sector may earn fewer revenues from these products. Declining revenues and other features of the animal pharma industry may lead to fewer research and development (R&D) dollars devoted to discovering and approving new antibiotics for use in food-animal production. This chain of events would lead to fewer antibiotics being sold, as well as fewer being developed.

¹“Food animal” is the animal pharma industry term for animals used to generate food. These foods include meat (including meat from poultry), dairy, eggs, and other animal byproducts. “Food animals,” therefore, encompass beef and dairy cattle, swine, poultry, as well as minor species like goats. Food animals are distinct from “companion animals,” which largely refers to cats and dogs.

Even as those forces suppress demand for antibiotics use in high-income countries, meat demand is growing globally. In particular, rising incomes and populations in low- and middle-income countries yield increasing demand for U.S. and European meat. Even if per-animal use of antibiotics declines in the United States and EU, the number of food animals may increase, potentially increasing U.S. and EU antibiotics sales.

These various pressures on overall sales of antibiotics may sway animal pharma's product development. If animal pharma moves out of supplying antibiotics, this has ramifications for agriculture. Veterinarians, producers, and other stakeholders in the livestock industry are concerned that fewer and fewer antibiotics are being developed for use in food animals. These stakeholders worry that a slowing pipeline of drug development would limit their ability to prevent and treat key, economically relevant livestock diseases (e.g., Ishmael (2017)). If true, it would have economic effects for the industry, which would be passed on to consumers as higher food prices.

While the topic is far-reaching and multidimensional, we restrict our focus to the following questions:

- What factors affect antibiotics *sales* in the United States and EU?
- What are the recent trends in antibiotics *sales* in agriculture in the United States and EU, and have sales reacted to policies?
- What are the trends in new pharmaceutical product and new antibiotic *development*?
- Have factors affecting demand for antibiotics *sales* influenced product *development*?
- Have regulations to curb antibiotic resistance affected the *development* of new antibiotics?

To further focus our analysis, we analyze the animal pharmaceutical industry's antibiotics market only from the perspective of the United States and EU. First, these two regions constitute a significant portion of the entire animal pharma market and global antibiotics sales for food-animal production. Approximately 60 percent of the global animal pharma market for all products (not just antibiotics) is in Western Europe or North America (IFAH, 2009).² Estimates of antibiotics use also suggest that the United States is the second largest user of antibiotics for food production (13 percent in 2010) behind China (23 percent in 2010), globally (Van Boeckel et al., 2015). Second, all of the leading animal pharma firms are headquartered in the United States or EU, and many products are initially aimed at these markets (and therefore these regions' regulatory processes). Third, these regions have a distinct set of challenges related to antibiotics sales, ones that may eventually occur elsewhere. Regulations of antibiotics use in food-animal production have been increasing in the United States and EU over the past several decades, and the United States in particular is seeing rising demand for "raised without antibiotics" production. Fourth, while China is the largest global producer of meat (27 percent of global production), the United States and EU are the second and third (15 and 13 percent, respectively, in 2015) (OECD-FAO, 2016). The United States and EU together constituted a third of the world's meat exports in 2016 (33.5 percent, OECD-FAO, 2016).

²The most recent public estimates from 2015 show that "Europe and the Americas" constitute 78 percent of the global market (for all products, not just antibiotics) (HealthforAnimals, 2015, website). However, "Europe and the Americas" includes South America and Eastern Europe. This finding suggests that "Western Europe and North America" could be accurately estimated to be 60 percent of the global market until at least 2015. Because the report excludes South America and Eastern Europe—focusing just on the United States and EU—we chose to use the older (more restrictive) 60-percent estimate.

Thus, what happens in these regions is an important indication of global trends in antibiotics use. Finally, the United States and certain European countries are among the limited number of nations with publicly available time series of antibiotics sales for use in food-producing animals.

While the United States and EU constitute large and important drivers of the animal pharma industry, other regions serve as important growth markets. Low- and middle-income countries have rising demand for and production of food-animal products, coupled with increasing use of veterinary interventions. In particular, China, India, and Brazil are predicted to rapidly increase their use of antibiotics for food-animal production (Van Boeckel et al., 2017). These areas may, therefore, become growth markets not only for agricultural antibiotics but also for other veterinary pharma products. Because of different climates, product approval procedures, intellectual property rights, livestock production methods, and other factors, these countries may have a large impact on the global animal pharma industry's structure and products developed. The major animal pharma firms that engage in research and testing have begun either partnering with domestic companies in these countries or otherwise entering these markets. Pharma firms that do not engage in research also operate in these regions. A variety of factors makes the animal health markets in these regions difficult to succinctly assess, and thus we largely do not consider them in this report. However, these regions are an important source for future analysis regarding trends in the animal pharma sector. Further, they serve as pivotal areas with regard to the spread of antibiotic resistance.

Antibiotics and Antibiotic Resistance: A Primer

What Are Antibiotics?

Microbes, including bacteria, can cause disease in humans and in animals. Antimicrobials are drugs or substances that can kill or impede growth of microbes such as viruses, fungi, parasites, and bacteria. Antibiotics are a subgroup of antimicrobials that kill or impede the growth of bacteria (specifically). Therefore, an antibiotic is also an antimicrobial, but not all antimicrobials are antibiotics.³ The first antibiotic, penicillin, was discovered in 1928 and was widely used during World War II to treat wound infections and prevent infections associated with surgeries (U.S. CDC, 2017).

Antibiotics are grouped into different classes according to type of bacteria they affect, their effect on bacteria, and their mode of action. Within each class, multiple antibiotics have been developed, which may be approved for use in humans, animals, or both. Antibiotic classes are pertinent to resistance development as well as regulatory efforts.

How Are Antibiotics Used in Human and Veterinary Medicine?

Antibiotics are used to prevent, control, and treat human and veterinary diseases. Notably, veterinary medicine includes companion animals (like dogs and cats) as well as food animals (like beef and dairy cows, poultry, and pigs). When treating animals for diseases, it may be economically viable and feasible to administer drugs to individual animals (via injection, feed, water, or other means). In certain food-animal-production scenarios, a farmer may treat (with veterinarian oversight) an entire herd when a disease is present among a few animals because it is not economically viable or feasible to individually diagnose and treat animals. Additionally, an individual or herd may be proactively treated, even before signs of infection are present because the herd is known to be a high-risk population (Sneeringer et al., 2015).

Antibiotics have also been used to promote growth in livestock in the United States since the 1950s (McEwen and Fedorka-Cray, 2002; Marshall and Levy, 2011; Moore et al., 1946), but this practice has been the subject of concern and subsequent regulation in many countries (see “U.S. and EU Regulations on Use of Antibiotics in Food-Animal Production,” p. 17). Growth-promoting uses of antibiotics have been linked to the development of antibiotic-resistant bacteria (Wegener et al., 1999; Smith and Crabb, 1957; Hershberger et al., 2005).

What Is Antibiotic Resistance?

Public health agencies describe antibiotic resistance as “one of our most serious health threats” (U.S. CDC, 2013, foreword) and “a global public health threat” (European Medicines Agency, 2018). In 2013, the CDC released a report that quantified the burden of antibiotic resistance in the United States for human medicine (U.S. CDC, 2013). This report estimated that antibiotic-resistant infections sicken 2 million people in the United States annually, of which 23,000 die. (This is approxi-

³Despite these differences, the terms “antimicrobials” and “antibiotics” are often used interchangeably. As a recent FDA document notes: “The term ‘antimicrobials’ refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobial drugs that have specific activity against bacteria are referred to as antibacterial or antibiotic drugs. However, the broader term ‘antimicrobial,’ commonly used in reference to drugs with activity against bacteria, is used ... interchangeably with the terms antibacterial or antibiotic” (U.S. FDA, 2012, p. 4).

mately the same number that died of Parkinson’s Disease in 2014 in the United States (Kochanek et al., 2016).) The same CDC report estimates the costs of these infections at \$20 billion to \$55 billion, through increased loss of life, extension of hospital stays, higher medical costs, and lost work productivity.⁴ Some estimates suggest that if no action is taken, antimicrobial resistance will cause more deaths than cancer by 2050 (Review on Antimicrobial Resistance, 2014).⁵

Antibiotic resistance occurs when bacteria develop the ability to resist the effects of an antibiotic. Resistance occurs when some bacteria in a population survive exposure to an antibiotic and continue to proliferate. Bacteria can have intrinsic resistance, which means that they have genes that naturally convey resistance to one or more antibiotics. They can also acquire resistance through the process of genetic mutation, or by incorporating foreign genes into their own genetic material through what is known as horizontal (lateral) gene transfer (Alekhshun and Levy, 2007).⁶

Any use of antibiotics in human medicine or in agriculture may accelerate the development of resistance by applying selective pressure to bacterial populations (Davies and Davies, 2010; U.S. CDC, 2013). Using a single antibiotic can contribute to the development of resistance to the same antibiotic, all antibiotics within the same class, or even antibiotics outside that antibiotic class. When resistance develops to one antibiotic in a class, this often results in resistance to some or all other antibiotics within the same class. This resistance can also occur across different antibiotic classes (Antimicrobial Resistance Learning Site, 2011).

Policy efforts aimed at antibiotics use in livestock production largely target antibiotic classes important for treating human disease; the U.S. Food and Drug Administration (FDA) terms these antibiotics “medically important” (U.S. FDA, 2018a). Antibiotics deemed by FDA to be “currently not medically important” have largely not been the subject of regulatory scrutiny. For example, ionophores are a class of antibiotics that are used only in animals, and ionophore use has not yet been shown to contribute to resistance to other classes of antibiotics (Callaway et al., 2003).

Scientists agree that use of antibiotics in food-animal production encourages antibiotic resistance. However, as Chang and coauthors (2015) note, “there are no data conclusively showing the magnitude of the threat emerging from agriculture.” Scientific understanding of how antibiotics use on farm is connected to clinically relevant human disease is complex and continually evolving. Scientific studies have posited and begun evaluating several mechanisms by which agricultural antibiotics use could encourage antibiotic-resistant infections in humans. Antibiotic-resistant bacteria

⁴These dollar values are extrapolated from the results of a single study. In this study, Roberts et al. (2009) used data from a hospital in Cook County, IL, to quantify the costs of antibiotic resistance. They found that having a resistant infection increased the risk of mortality and extended the duration of hospital stays by between roughly 6 and 13 days. The total costs presented in the CDC report are presented in a 2010 fact sheet from the Alliance for the Prudent Use of Antibiotics (APUA, 2010). In that fact sheet, they multiply the estimated per-patient medical costs attributed to resistance and cost of lost wages due to a longer hospital stay from Roberts et al. (2009) by the estimated number of antibiotic-resistant infections in the United States in the year 2000 (900,000) to arrive at estimates of total direct health care costs of \$20 billion, and additional costs due to lost productivity of \$35 billion. Other studies support the finding that resistant infections increase the risk of death and increase the length of hospital stays (e.g., Nathwani et al., 2014), but many articles that quantify the economic costs of these findings do not adequately control for other factors that are associated with resistance and/or cost of treatment. (See Larson, 2010, for a review of the literature.)

⁵Notably, this estimate for the number of deaths has been critiqued as “uncertain” (Kraker et al., 2016). However, even the authors of the critique state that “urgent action” is required to confront antimicrobial resistance.

⁶Horizontal gene transfer can occur via *transformation* (the bacterium takes DNA from the environment into their own genome); via *transduction* (a bacteriophage, a virus that infects a bacterium, can transfer its DNA to the bacterium); or via *conjugation* (bacteria can transfer genes to other bacteria, even to different types of bacteria) (Alekhshun and Levy, 2007).

persist in animal manure, which may then be spread on fields, after which it may run off into streams, enter groundwater, and possibly even contaminate agricultural produce (Chee-Sanford et al., 2009; Marti et al., 2013; Wellington et al., 2013).

Resistant bacteria can also travel through the air, be released into the environment when animals are shipped, and colonize livestock or processing plant workers who interact with their family or their community (Price et al., 2007; Rule et al., 2008; Marshall and Levy, 2011; Rinsky et al., 2013; Smith et al., 2013; Castillo Neyra et al., 2014). The genes that carry resistance can also spread within the environment—from one bacterial species to another, as well as through other pathways (Alekshun and Levy, 2007). Finally, resistant bacteria may be present on retail meat and poultry products (Chen et al., 2013; Ge et al., 2013; Sjölund-Karlsson et al., 2013; Zhao et al., 2015; Liu et al., 2018). Foodborne bacteria such as salmonella and campylobacter can cause illness (Scallan et al., 2011), and these illnesses have associated costs (Hoffman et al., 2012). Resistant foodborne bacteria have the potential to make foodborne illness more costly or difficult to treat. Increased use of whole-genome sequencing is improving the ability to track and analyze patterns of resistance and their origins (Karp et al., 2017).

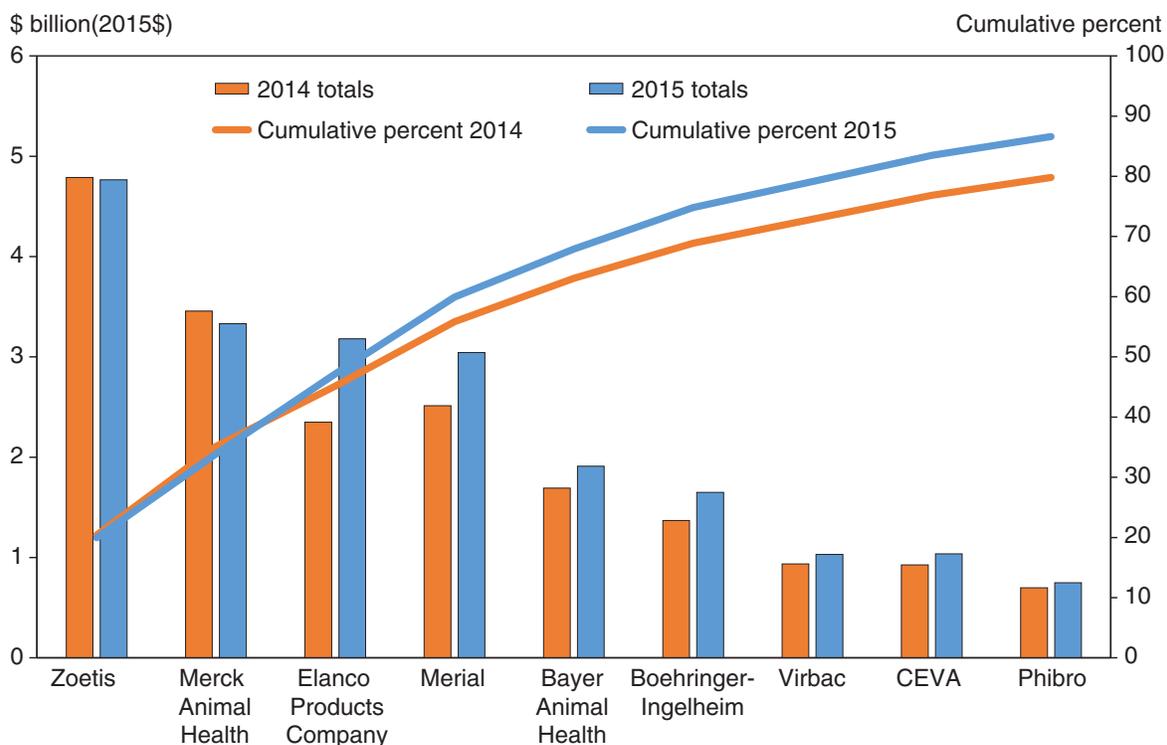
The Animal Pharmaceutical Industry: Background

Animal pharma researches, develops, and markets drugs, biologics, and pesticides for use in companion and food animals. The industry generates an important input for agricultural productivity and conducts research as intensively as the biotech, seed, and pesticide industries (Fuglie et al., 2011).

Size and Structure

Global animal pharma industry sales steadily grew from \$18.5 billion in 2005 to \$24.2 billion in 2015 (in real 2016 U.S. dollars) (HealthforAnimals, 2015; IFAH, 2006). Growth rates in that time averaged 2.7 percent per year. Animal pharma industry sales are dominated by nine large companies, which sold about \$21 billion in animal pharma products (87 percent of total animal pharma sales) in 2015 (fig. 1). Even between 2014 and 2015, the industry’s concentration increased; from 2014 to 2015, the top nine firms’ share of total animal pharma sales grew from 80 percent to 87 percent. The industry is becoming more concentrated through mergers, with potential ramifications for research. (See box “Impact of Market Concentration on Innovation.”)

Figure 1
Major animal pharmaceutical companies’ sales and cumulative percentage of global industry sales, 2014 and 2015



Note: Sanofi sold its animal health business (Merial) in 2017 to Boehringer-Ingelheim. Chart predates this merger.
 Sources: USDA, Economic Research Service calculations from company annual reports for 2014 and 2015; Bayer (2014, 2015); Boehringer-Ingelheim (2014, 2015); CEVA (2014, 2015); Eli Lilly and Co. (2014, 2015); Merck & Co., Inc. (2015, 2016); Novartis (2014; 2015); Phibro (2015, 2016); Sanofi (2015, 2016); Virbac (2015, 2016); Zoetis (2014; 2015). Total sales are from HealthforAnimals, 2015 and 2013. Total sales for 2014 are not reported; thus, the total is a linear extrapolation of totals for years 2013 and 2015. Dollar values are in real terms for 2015.

Impact of Market Concentration on Innovation

The effect of greater concentration in animal pharma on innovation in the sector is uncertain. Increased concentration can increase or decrease research and development (R&D) (Shapiro, 2012). For example, suppose there are a lot of drug makers and customers are somewhat loyal to individual brands. If each drug maker is very small, it may lack the resources to conduct costly R&D. If the drug maker can hope to sell to only its small slice of the market, it might not have an incentive to conduct R&D in any case. In this situation, mergers and other increases in concentration might increase R&D by enabling larger firms to sell to larger markets. On the other hand, in the extreme case with just one drug maker, any new drugs the firm invents mostly serve to cannibalize the sales of its own existing products.

This scenario may produce very low incentives to do R&D, so increasing concentration from two firms to one might decrease R&D. Furthermore, in the case of the animal pharma industry, spokespeople note that consolidation yields less expertise by type of drug (Shryock, 2004; Brown, 2011). For example, if two firms each have a staff of 100 researchers searching for new antibiotics, and the two firms merge, the new firm may retain only 150 researchers. Moreover, in the human pharmaceutical industry, consolidation has been linked to less research for new antibiotics (Pidcock, 2012).

Although the industry operates globally, with many firms having branches in multiple countries, 60 percent of sales were in North America and Western Europe (IFAH, 2009).⁷ By itself, the United States encompasses one-third of global animal pharma sales (Pham and Donovan, 2018). Leading animal pharma firms are headquartered in the United States or EU, and many products are initially aimed at these markets.

Besides the major firms, other types of firms operate in the industry. While the major firms may market generic products and perform R&D, other firms may just manufacture generic (off-patent) material. Others focus just on generic formulations (Gerecke, 2006).

Connections Between the Human and Animal Pharmaceutical Industries

The animal and human pharmaceutical industries share many features. Their R&D techniques resemble one another and 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 (in human pharma, prescriptions from doctors; in animal pharma, prescriptions or veterinary feed directives from veterinarians). Although animal pharma is a large global presence, it is small in comparison to human pharma. In 2014, human pharma realized nearly \$1 trillion in sales (IMS Health Market Prognosis, 2015), 42 times that of animal pharma sales (\$23.9 billion) (HealthforAnimals, undated).

⁷Later estimates are not broken down with as much country precision. In 2015, 78 percent of sales were in the Americas and Europe. The Americas include Latin America as well as North America, and Europe includes both Western and Eastern (HealthforAnimals, 2015).

In 2015, six of the top seven animal pharma companies were divisions of human pharma companies, and the biggest company by sales, Zoetis, was only recently independent from its human pharma parent Pfizer. One source of novel animal health compounds traditionally is the “cast-offs” from parent company human health discovery (Shryock and Richwine, 2010). 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 (for example, they fail toxicology requirements). 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.

Types of Products

The animal pharma industry does not cover just *food*-animal agriculture. In 2016, 64 percent of global industry sales for all products from the animal pharma industry were for food-animal production, while 36 percent were for *companion* animals. Interestingly, the U.S. shares for these two animal types reflect virtually the reverse of the global shares; in 2016, 60 percent of U.S. sales were for companion animals, while 40 percent were for food animals (Pham and Donovan, 2018). In the most recent year with statistics with sales by specific livestock types (2009), the largest share of sales for global food-animal production was for cattle (25.1 percent), followed by pigs (17.6 percent) and then poultry (11 percent) (IFAH, 2009).⁸

Animal pharma generates products that it roughly groups into three categories. These include pharmaceuticals, biologics, and medicinal feed additives.⁹ Any of these may be developed for companion or food animals.

- **Pharmaceuticals** include anti-infectives like antibiotics as well as parasiticides, exogenous hormones, and other products. “Pharmaceuticals” are alternatively called “pharmaceutical drugs” or simply “drugs.” FDA describes a drug as an “article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.”
- **Biologics** are largely vaccines.¹⁰ FDA defines veterinary biologics as “all viruses, serums, toxins, or analogous products of natural or synthetic origin which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response” (U.S. FDA, 2017a).
- **Medicinal feed additives** include amino acids, antibiotics, vitamins, antioxidants, feed enzymes, and other products that are added to feed; these products make drug claims and are therefore regulated as such. Other nonmedicated feed additives do not make drug claims and are therefore not referred to as “medicated.” The nonmedicated feed additives include vitamins and minerals and are largely not sold by animal pharma.

⁸Food-animal products constituted 58.2 percent of sales in 2009; in addition to cattle, pigs, and poultry, sheep constituted 4.5 percent of food-animal product sales.

⁹Perhaps confusingly, the “pharmaceutical” industry generates things other than pharmaceuticals.

¹⁰Biologics also include “bacterins, allergens, antibodies, diagnostics, antitoxins, toxoids, immunostimulants, antigenic or immunizing components of microorganisms intended for use in the prevention, diagnosis, management or cure of disease in animals” (U.S. FDA, 2017a).

Thus, antibiotics are subsets of the categories of “pharmaceuticals” and “medicinal feed additives.” In 2017, pharmaceuticals comprised the largest share of animal pharma industry sales (58 percent). Biologicals were estimated at nearly a third of sales (30 percent), and medicinal feed additives comprised 12 percent (HealthforAnimals, 2018).

How much revenue does animal pharma get from antibiotics? Animal Pharm, a data collection and consulting firm, reported that in 2017 animal pharma companies generated \$5 billion in revenue from antibiotics for food animals (Watt, 2018, citing Animal Pharm). This would constitute approximately 19 percent of global annual sales in the animal pharma industry (using a \$26 billion estimate of 2017 global industry sales).¹¹

Annual company reports also indicate the importance of antibiotics to revenue streams in animal pharma firms. Because of new U.S. regulations fully enacted in 2017, many company reports included sections on how much of a risk this regulation would pose to their revenues. Table 1 provides, for some major animal pharma firms, the shares of total revenue earned from antibiotics, antibacterials, and even certain antibiotic products, and these shares are significant.

Table 1
Indications of the importance of antibiotic sales to animal pharmaceutical firm revenues

Company	Indications of percentage of sales in antibiotics
Zoetis	Zoetis states that in 2016 its revenue attributable to antibacterials for livestock was \$1.3 billion. The company's total revenues for the year were \$4.9 billion, suggesting that 27 percent of its revenues were from antibacterials (Zoetis, 2017).
Bayer	Bayer markets Baytril®, which is a medically important antibiotic used in cats, dogs, cattle, and swine. According to Bayer's 2017 annual report, Baytril® sales totaled €113 million (\$140 million) in 2016 while total animal health sales totaled €951 million (\$1,177 million). Thus Baytril® by itself constituted 12 percent of Bayer's animal health sales (Bayer, 2017); the total revenue share for Bayer in antibiotics for animals may be larger.
Virbac	Virbac's 2016 annual report states that its bovine and pig antibiotics sales totaled €111.3 million (\$138 million), which constituted 31 percent of all product sales for food-producing animals (Virbac, 2016). Between 2012 and 2016, Virbac's sales of bovine and pig antibiotics have been slowly rising (from €102 million in 2012), but falling as a share of product sales in food-producing animals (from 39.3 percent in 2012) (Virbac, 2013 and 2017).
Vetoquinol	Vetoquinol states that in 2016, 32.6 percent of its global sales were in antibiotics; this is down from 43.1 percent of its sales in 2011 (Vetoquinol, 2017).
Phibro	Phibro states that in 2016, \$37 million of its sales were in medically important antibiotics. In 2017, that number was \$23 million (Phibro, 2017, p. 17). Phibro's total sales in animal health for 2016 and 2017 were \$486 million and \$498 million, respectively, suggesting that medically important antibiotics sales constituted 7.6 percent and 4.6 percent of sales in 2016 and 2017 (Phibro, 2016, 2017).

Note: Conversion factor for euros to U.S. dollars used is € = \$1.24.

Sources: USDA, Economic Research Service compilation from company annual reports (noted in table).

¹¹We can also look to other sources to attempt verification of the \$5 billion number constituting around 19 percent of the global market. A 2004 publication from an industry employee notes that 26 percent of the global animal health market derives from antimicrobials (Shryock, 2004). The animal pharma industry group HealthforAnimals publishes statistics on the percentages of global revenues by product category, but after 2009 these categories covered only the major three of pharmaceuticals, biologics, and medicinal feed additives. In the most recent year of statistics with further disaggregation (2009), 15 percent of sales were for anti-infectives while 12 percent were in medicinal feed additives. However, not all medicinal feed additives or anti-infectives are antibiotics, so 27 percent serve as an upper bound.

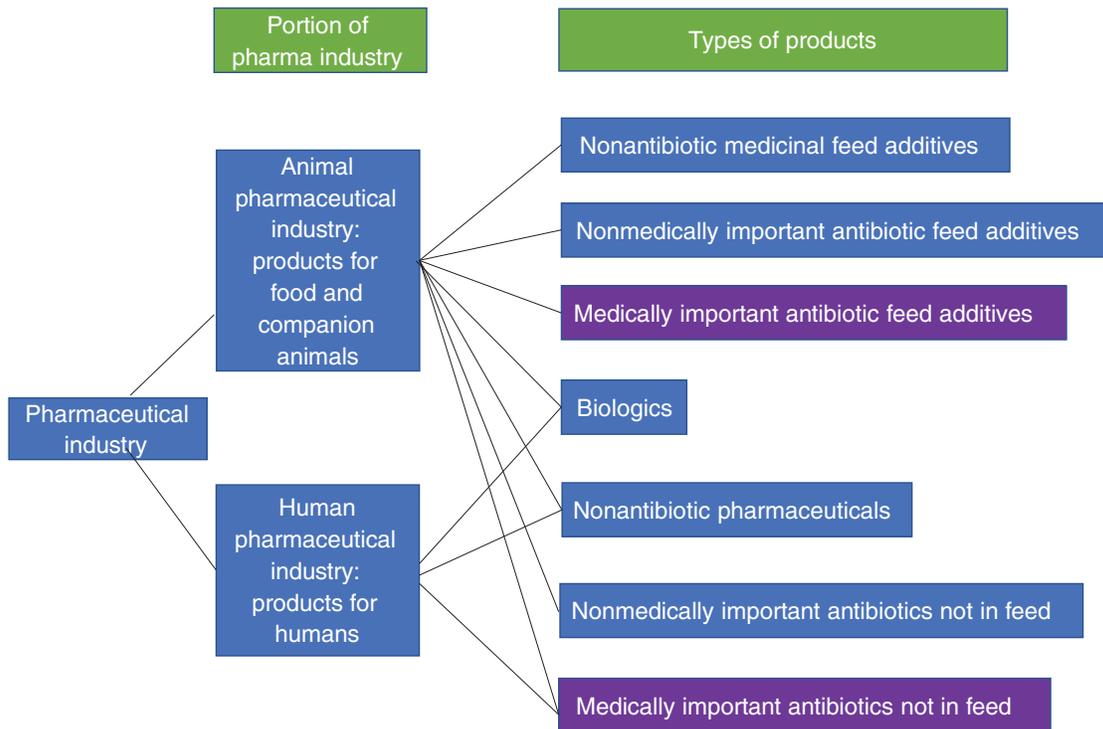
Overlap of Product Types Between Human and Animal Pharmaceuticals

Human and animal pharma develop similar types of products—a fact that is pertinent not only for R&D but also antibiotic development (fig. 2). Both human and animal pharma generate pharmaceuticals and biologics (e.g., drugs and vaccines), but human pharma does not have a regulatory category specifically for pharmaceutical feed additives. Pharmaceuticals for human use can be divided into antibiotics and non-antibiotics. Like pharmaceuticals for human use, animal pharmaceuticals are also divided into antibiotics and non-antibiotics; medicinal feed additives can be antibiotics or not. Animal antibiotics can be further subdivided into “medically important” (i.e., pertinent in treating human disease) and “not currently medically important.”

These overlaps in product types means that animal pharma has been able to use R&D aimed at human product development. Animal pharma relies on human pharma for innovations because the large human market can support more expensive health R&D. Animal pharma’s dependence on human drug discovery, however, 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 are easily applied to animal health, but when the two separate, it is difficult for animal pharma to conduct discovery research on its own to fill the void.

Figure 2

Schematic of pharmaceutical industry divisions and products developed



Source: USDA, Economic Research Service.

In relation to antibiotics, human pharma has been developing fewer of these drugs in recent decades, causing increasing concern (Theuretzbacher, 2015). Shifts away from the discovery of novel antibiotics in human pharma may make it correspondingly more difficult for animal pharma to develop its own antibiotics.

Product Development and Approval Process

The process of product development is long and complicated. Accordingly, a company must decide carefully where to place its research dollars. A new product passes through multiple phases (discovery, development, and registration) before it comes to market, and there is significant attrition of potential product candidates in the pipeline (Hunter et al., 2011). Development of a new animal drug is estimated to take 7 to 10 years, while development for a new veterinary vaccine ranges between 3 and 5 years (Animal Health Institute, undated).

Regulatory approval for animal health products in the United States is divided between FDA, USDA, and the Environmental Protection Agency (EPA). USDA's Animal and Plant Health Inspection Service Center for Veterinary Biologics (APHIS CVB) oversees the regulation of veterinary biologics; EPA oversees products deemed pesticides, while FDA's Center for Veterinary Medicine (FDA CVM) governs the regulation of conventional drugs¹² and dietary supplements (Hunter et al., 2011). Conventional drugs are typically chemically synthesized with known structures, while biologics (such as vaccines) refer to biological products that are usually complex mixtures that are not easily characterized. Antimicrobials fall under the purview of FDA's regulation.

In general, to receive drug approval from FDA CVM, the product's sponsor must file information on the drug's chemistry and composition, the proposed labeling, and evidence demonstrating three things (Meyer, 2014). First, the drug must be *effective* in doing what it proposes to do on its label. Second, the sponsor must be able to *consistently manufacture* the product with good practices. Finally, the drug must be *safe* for the animal, the environment, and people, when used as directed on the label (U.S. FDA, 2015). Further testing is required for the approval of new antibiotics. Once a drug has cleared registration, its application is referred to as an approved New Animal Drug Application. Registration in the United States typically takes more than 7 years for a food-animal drug product. Given that the discovery phase often takes 2-3 years, product development generally takes 10 years or more in the United States to move a product from an idea to the market (IFAH, 2012).

In broad strokes, the approval process for veterinary biologics resembles the process for pharmaceutical drugs. Applicants must demonstrate that their product is safe (for animals and human handlers or consumers), effective, and compliant with manufacturing criteria (USDA, APHIS, 2011). APHIS CVB approves licenses for veterinary vaccines, diagnostics of biological origin, and other products.

Health products may also be delivered in animal feed as a "feed additive." If the product is a drug or biologic, then it is regulated as such, regardless of the fact that it is delivered in food. However, FDA also regulates feed additives that do not make a medical claim (for example, vitamins, essential oils, or herbal supplements), but under a different set of criteria. Additives with an intended use already approved by FDA, or additives that are "generally recognized as safe" (GRAS)¹³ do not need to seek

¹²FDA considers a drug to be any product intended for use in diagnosing, curing, mitigating, treating, or preventing disease.

¹³Additives for which there is a broad scientific consensus about safety are GRAS. FDA has a list of products it has designated as GRAS, and there is a notification process to add new substances to this list.

additional approval for use. Otherwise, FDA approval must be sought for the new additive or use. This typically involves showing the proposed use of the additive is safe, but does not require proving any claims about efficacy.

Because a significant portion of animal pharma sales are earned outside the United States, regulatory approval is an international activity. For conventional drugs, the two most important regulatory authorities are FDA in the United States, and the European Medicines Agency in the EU (Hunter et al., 2011). Rather than developing national regulations from the ground up, most other countries' regulatory agencies will refer to FDA, European Medicines Agency, or other international animal health entities such as the World Organization for Animal Health or the Codex Alimentarius (Zoetis, 2014). Certain testing requirements are also harmonized across the EU, United States, and Japan through the Veterinary International Conference on Harmonization (VICH). Nonetheless, approval must still be sought from each regulatory agency, and often applications will require country-specific evidence (especially if climatic conditions are very different) (Meyer, 2014).

Patents and Generics

Firms may seek to protect their product with a patent. Patents are generally country-specific with patent protection having to be sought in each country where a product is registered. While regulatory approval gives firms the right to market products, a patent gives them the right to exclude others from marketing a similar product for a specified length of time. Patents are granted on a first-to-file basis, which provides a strong incentive for firms to file as soon as they have identified a viable product. At the same time, patents typically grant market exclusivity for 20 years, much of which time will be spent securing regulatory approval to market the product. In addition to patents, regulatory agencies may also provide shorter windows of market exclusivity to qualifying products. For example, an animal pharma product that has not been previously approved (i.e., for other species or indications) is eligible for 5 years of market exclusivity from FDA. During this period, which starts when the drug is approved, FDA will not accept applications for generic versions of the drug (U.S. FDA, 2018b).

Once a product loses patent protection, rivals are free to develop generic alternative versions. In human pharma, this is associated with a substantial decrease in sales of the original drug. The decrease in sales in animal health is less severe, although this varies by market. Generics account for just 10 percent of dispensed animal health products, and no large, well-capitalized global company focuses on animal generics (PWC, 2015). Any prospective generic entrant also needs to obtain regulatory approval. In the United States, generic approval for veterinary drugs began in 1988, with the first generic drugs marketed in 1992 (U.S. FDA, 2018c). Generic approval requires showing a drug is identical¹⁴ to the originally approved drug, but does not require reestablishing the safety and efficacy of the drug in new clinical trials. Biologics do not have a similar generic process.¹⁵

¹⁴The exact requirement is to prove “bioequivalence,” defined by FDA as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study” (U.S. FDA, 2003a).

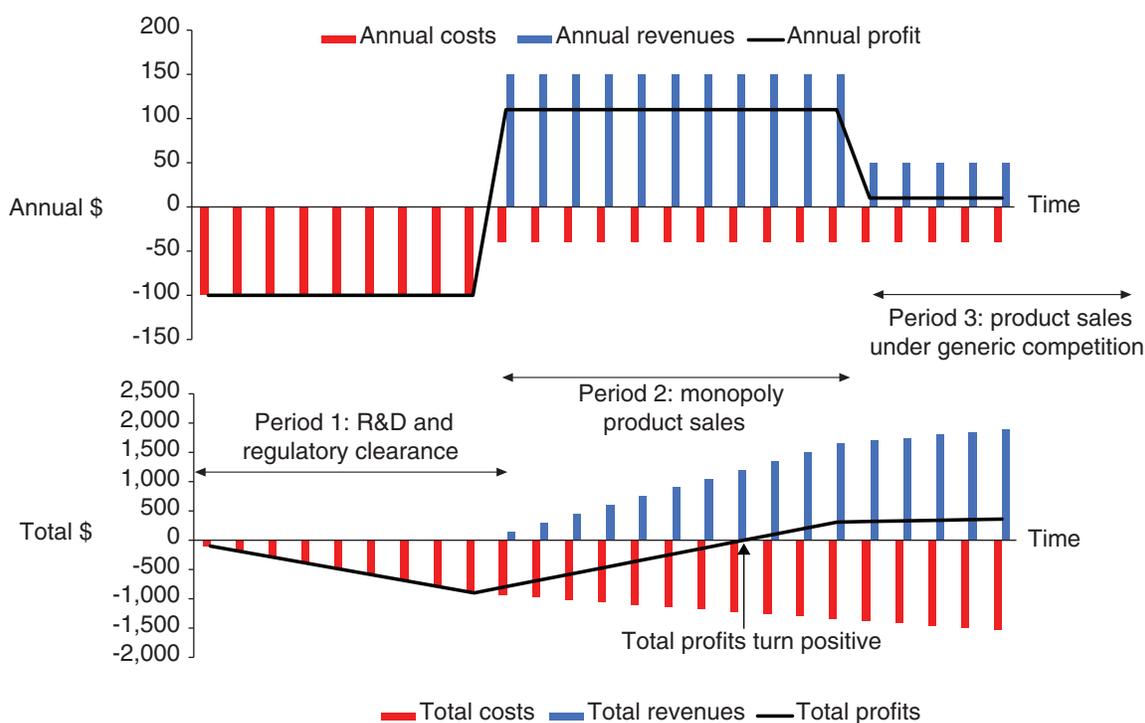
¹⁵For human biologics, there is an abbreviated approval process for “biosimilars,” which FDA describes as “biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-approved biological product” (U.S. FDA, 2018f). A similar mechanism is not available for veterinary biologics.

Costs, Revenues, and Profits Over a Drug's Lifetime

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.

Figure 3 depicts the costs, revenues, and profits of a drug over its lifetime. The top panel depicts the *annual* costs, revenues, and profits, while the bottom depicts *total* costs, revenues, and profits. There are three distinct periods in a drug's life. In period 1, the drug maker conducts R&D and seeks regulatory approval. During this period, the drug maker endures high annual costs and has no revenues because the drug is not yet approved for sale. At the end of this period, the drug maker has made a high investment, and the drug's profits are far below zero. Once the drug obtains regulatory approval, it enters period 2. In most cases, the drug will enjoy a temporary monopoly position (due to patent protections, FDA market exclusivity, and time required for rival firms to enter the market). Revenues during this period are high, and costs fall to equal the costs of drug manufacturing. (We have illustrated these as being lower than the cost of R&D in period 1.) Annual profits are given as the difference between revenues and costs. During period 2, annual profits will be large and positive (the top panel). However, total profits (the bottom panel) may not turn positive until late into this period, because it will take time to recoup the R&D costs of period 1.

Figure 3
Stylized costs, revenues, and profits over a drug's lifetime



Source: USDA, Economic Research Service.

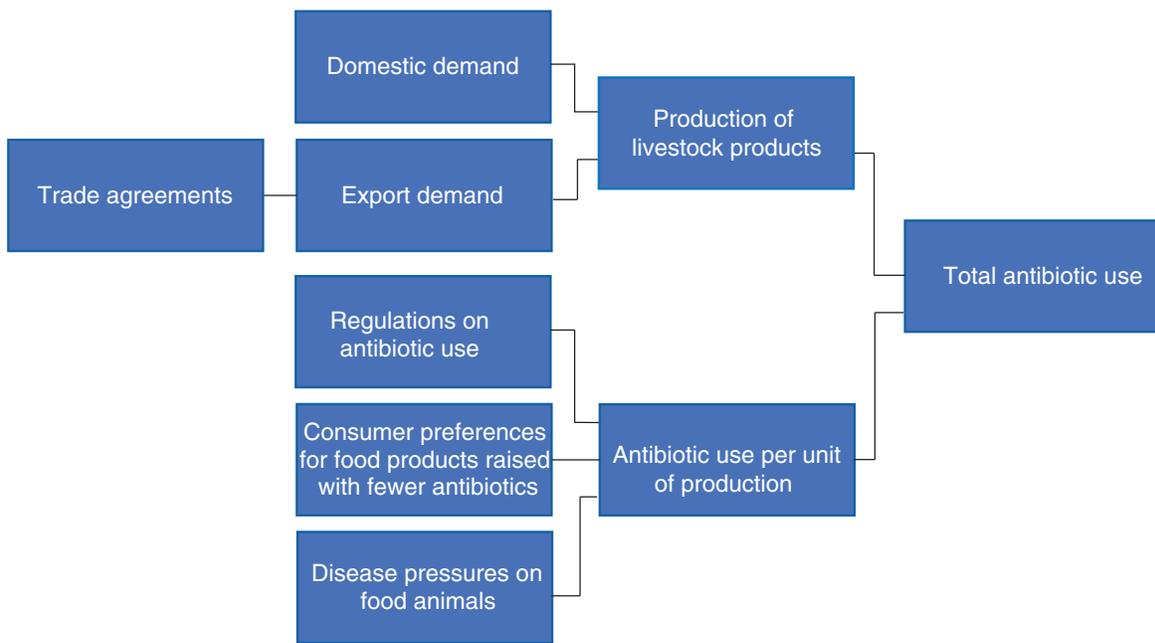
Finally, at some point, a generic competitor may enter the market and the drug enters period 3. During this period, the drug's manufacturing costs do not necessarily change, but the drug maker may have to compete with the generic competitor by offering lower prices. We have illustrated this as a drop in annual revenues, with no change in annual costs. Annual profits are the difference between revenues and cost, and in period 3, they fall sharply, in this example.

To summarize, although the drug maker may have large revenues relative to production costs in period 2, the total profitability of the drug over all three periods takes into account the large R&D costs of period 1 and may be significantly lower.

Factors Driving Sales of Antibiotics in U.S. and EU Food-Animal Production

The animal pharmaceutical industry obtains a significant share of its revenues from antibiotics for food-animal production. What happens to that revenue stream depends on the drivers of demand for antibiotics use in food-animal production. Broadly, we can decompose the quantity of antibiotics sales for food-animal production into a function of the number of animals on which antibiotics are potentially used and the use per animal (fig. 4). Demand for animal products will be a function of both domestic and export demand, but the amount exported will be affected by trade agreements and restrictions. Use of antibiotics on a per-food-unit basis is a function of regulations, consumer preferences for products raised with fewer antibiotics, and disease pressures. Disease pressures may increase or decrease, with attendant changes in antibiotics use.

Figure 4
Factors in country-level demand for antibiotic use in food-animal production



Source: USDA, Economic Research Service.

U.S. and EU Regulations on Use of Antibiotics in Food-Animal Production

Regulations on the use of antibiotics in food-animal production is one factor influencing sales of antibiotics. Because of concerns about the relationship between use of antibiotics in livestock and the development of antibiotic resistance relevant to human medicine, many countries have restricted antibiotics use in livestock. Regulations typically target specific classes of antibiotics, routes of administration of antibiotics (in feed, water, or via injection), or purposes for antibiotics use (e.g., for growth promotion or disease prevention). The path of regulation of antibiotics use in livestock has differed, depending upon the country.

The United States has directly restricted the use of some classes of antibiotics in food-producing animals since the 1990s (see table 2). In 2017, Guidance for Industry #213 and the revised Veterinary Feed Directive were implemented (U.S. FDA 2012a, 2013). Originally announced in 2013, they made it illegal to use antibiotics important to human medicine for production purposes (growth promotion or improved feed efficiency), and brought other feed and water uses of medically important antibiotics under veterinary oversight. In the final year before the guidances took full effect (2016), 96 percent of medically important antibiotics approved for use in food-producing animals were sold over the counter (U.S. FDA, 2017b).¹⁶

Table 2

Timeline of regulation of antibiotic use in food-producing animals in the United States

Year	Event
1997	FDA prohibits extralabel use of fluoroquinolones and glycopeptides in food animals.
2005	FDA withdrawals approval of the use of fluoroquinolones in poultry.
2012	FDA bans some extralabel uses of cephalosporins in food animals.
2013	FDA publishes final Guidance for Industry #213, which eliminates the use of medically important antibiotics for production purposes, and requires veterinary oversight to use medically important antibiotics for other purposes.
2015	FDA publishes Veterinary Feed Directive final rule, which establishes a framework for veterinarians to authorize the use of medically important antimicrobials in animal feed for therapeutic purposes.
2017	VFD final rule and Guidance for Industry #213 are implemented.

Note: FDA = U.S. Food and Drug Administration. VFD = Veterinary Feed Directive. This table includes only regulatory actions that restricted use of approved antibiotics in food-producing animals. Other regulations have been adopted related to initial approval of antibiotics for use in food-producing animals.

Sources: U.S. Food and Drug Administration's "Timeline of FDA Action on Antimicrobial Resistance" and "FACT SHEET: Veterinary Feed Directive Final Rule and Next Steps" (both available online).

¹⁶Two U.S. States have added additional restrictions on use of antibiotics for preventive purposes. California and Maryland both adopted stipulations that are meant to reduce preventive use of antibiotics (California Senate Bill No. 27, 2015; Maryland Keep Antibiotics Effective Act of 2017). Both rules went into effect in the same time frame as the new Federal rules, and confusion remains as to how these rules differ from the Federal ones. One goal of the State rules was to stop livestock producers from switching their medically important antibiotics use from "growth promotion" (no longer allowed under the Federal rules) to "preventive use" (still allowed under the Federal rules). However, both State rules still allow for preventive use. For example, the California law allows for the administration of a medically important antibiotic to "treat, control, and, in some cases, prevent, disease" (California Senate Bill No. 27, 2015).

Countries in the EU began regulating use of antibiotics much earlier than the United States (table 3). An EU-wide ban on antibiotics use for growth promotion went into effect in 2006 (U.S. GAO, 2011).

Table 3

Timeline of withdrawal of antibiotics for various agricultural purposes in European Union countries

Year	Event
1986	Sweden bans use of antibiotics for growth promotion.
1988	Sweden stops use of all general prophylactic medications.
1994	Denmark restricts direct sales of antimicrobials from veterinarians and limits veterinary profits from antibiotic sales. Denmark bans routine prophylactic use of antibiotics.
1995	Denmark bans use of avoparcin.
1996	Germany bans use of avoparcin.
1997	European Union bans use of avoparcin. Netherlands bans use of olaquinox and carbadox.
1998	Denmark bans use of virginiamycin.
1999	European Union bans olaquinox and carbadox; suspends authorization of bacitracin, tylosin, spiramycin, and virginiamycin. Sweden bans use of flavophospholipol and avilamycin as growth promoters. Denmark’s swine industry voluntarily stops use of all antimicrobial growth promoters.
2006	European Union bans all antibiotics for growth promotion. Germany prohibits use of antibiotics needed as a result of “rearing conditions.”
2008	Netherlands’ livestock industry adopts voluntary guidelines to reduce antimicrobial use.
2009	Netherlands adopts compulsory 50% reduction in antimicrobial livestock use between 2009 and 2013.
2010	Denmark adopts “yellow card” policy, which gives warnings to cattle and pork producers if they exceed a threshold of antibiotic use per animal.

Source: USDA, Economic Research Service developed from a similar table in Cogliana et al. (2011).

Changes in Consumer Preferences for Meat and Poultry Products “Raised Without Antibiotics”

Consumer and retailer demands for reduced antibiotics use have also been a driver for lower antibiotics sales. In the early 2000s, a number of companies began offering meat and poultry products that were labeled as “raised without antibiotics.”¹⁷ Between 2000 and 2017, the number of different brands offering “raised without antibiotics” chicken (including organic brands) grew from around 13 to over 130.¹⁸

¹⁷For the purposes of this report, we use “raised without antibiotics,” or “RWA,” to refer to livestock and poultry products where the source animals have not been administered any antibiotics (including ionophores) via any route from birth to harvest. Other commonly used label terms connote the same production practice. Other similar labels include “No Antibiotics Ever,” “No Antibiotics Added,” and “No Antibiotics Administered” (USDA, FSIS, 2016; USDA, FSIS, 2017). To use one of these labels, producers must present documentation to the USDA’s Food Safety and Inspection Service (FSIS). We use the phrase “raised with antibiotics” to cover any of these established labels.

¹⁸ERS analysis using data from Label Insight, USDA, Food Safety and Inspection Service, and IRI Consumer Panel. For more information about the IRI data, see Muth et al. (2016). “IRI” previously stood for “Information Resources, Inc.,” but now the company uses just the acronym “IRI.”

The rise of “raised without antibiotics” production in the United States has been led by key players in the poultry industry. Perdue Foods is the fourth largest U.S. chicken company, producing 12.98 million broilers in 2016 (Watt PoultryUSA, 2017). In fall 2016, the company announced it had eliminated all antibiotics use except to treat disease, and it estimates that approximately 3 percent of their birds are eventually treated for illness. Those that are treated are sold under different (non-Perdue) product lines. Tyson Foods, the country’s largest broiler producer, followed suit, and announced that it would be eliminating all antibiotics except for disease treatment in 2017. As a result of these efforts and those of a number of smaller firms, 44 percent of the U.S. broiler market was being raised without antibiotics in 2017, up from 2.7 percent in 2012.¹⁹ Producing broilers without antibiotics requires careful management and some changes in practices, but most broilers that are raised without antibiotics are still raised in poultry houses using production practices similar to conventional production (Bowman et al., 2016).

A number of factors make a similar transition less likely in hog and beef cattle production. The costs associated with raising broilers without antibiotics are lower than the costs of raising hogs or beef cattle without antibiotics, in part because of chickens’ shorter production lifecycle and attendant reduced disease likelihood. Nonetheless, several major players in the pork and beef industries such as Cargill, Tyson, and Smithfield began to offer “natural” product lines in recent years that are also raised without antibiotics (Pew Charitable Trusts, 2016).²⁰ Some retail and fast food chains have also made commitments about sourcing pork and beef that use fewer antibiotics (Natural Resources Defense Council, 2017).

“Raised without antibiotics” production is currently largely for domestic consumption. However, some of the countries to which the United States exports have nascent niche markets for meat and poultry products raised without antibiotics. For example, niche markets for pork raised without antibiotics are emerging in high-income urban areas in China, in part due to concerns about rising rates of antibiotic resistance, China’s use of antibiotics in meat production, and food safety (Bloomberg News, 2016).

Changes in Disease Pressure in Livestock Production

Medically important antibiotics are no longer used for growth promotion or other production purposes in the United States or EU, but may still be used for disease prevention, control, and treatment. Reducing the introduction and spread of diseases on-farm will reduce the need for antibiotics, particularly for prevention purposes. Livestock production in the United States and Europe is, for the most part, highly industrialized and modernized, and the shares of production using various methods of biosecurity and disease-threat-reduction practices have been increasing. Regulations or consumer pressures may encourage the adoption of disease reduction practices, but producers may also adopt these practices if they find them cost-beneficial.

¹⁹Personal communication with Michael Sheats, USDA, Agricultural Marketing Service. This statistic does not include USDA-certified organic broilers, which also do not use antibiotics ever. However, in every year between 2012 and 2017, organic broilers constituted less than 1 percent of all birds.

²⁰The use of the term “natural” on meat and poultry labels is used as follows, as specified by USDA’s Food Safety and Inspection Service: “A product containing no artificial ingredient or added color and is only minimally processed. Minimal processing means that the product was processed in a manner that does not fundamentally alter the product. The label must include a statement explaining the meaning of the term ‘natural’ (such as ‘no artificial ingredients; minimally processed’).” However, a number of products and brands still label and name products using the term “natural,” intending the common and historic usage of the term (e.g., Matthews and Johnson, 2013).

Disease threat-reduction practices vary across species and stage of production. Describing all of them is outside the scope of this report. Table 4 provides some indications of changing management practices that can reduce disease threats and thereby antibiotics use. In swine, these practices include the adoption of Pork Quality Assurance (PQA) Plus plans, written biosecurity plans, and the cleaning of vehicles used to transport animals. PQA and biosecurity plans can help to reduce disease threats from visitors, employees, and pests. The cleaning of transport vehicles can reduce the probability of transmitting bacteria between animals. In the table, these practices all cover an increasing share of hogs between 2009 and 2015.

As described above, the broiler industry has seen a rising share of “raised without antibiotics” production. In part, this increase is enabled by the relatively widespread adoption of biosecurity practices in the industry. Table 4 shows four measures that might yield a lowering of antibiotics use. First, a Hazard Analysis and Critical Control Point (HACCP) program includes biosecurity practices to reduce disease threats. Although animal welfare requirements do not specifically target disease reduction, they often include increasing the space per animal; reductions in stocking density have been linked to lowering antibiotics use (e.g., Guardia et al., 2011). Newer barns with temperature controls in the form of evaporative cooling and tunnel ventilation can also reduce stress in the birds, yielding better health profiles. All of these practices increased between 2006 and 2011.²¹

Table 4

Selected indications of changes in food-animal management practices for hogs, broilers, and beef that may lessen use of antibiotics

Hogs		
Percentage of hog animal units* produced at a facility with...	2009	2015
A Pork Quality Assistance (PQA) Plus certification	81	91
A written biosecurity plan	64	83
Vehicles used to transport hogs cleaned and disinfected before loading hogs	80	85
Broilers		
Percentage of broilers raised at a facility with...	2006	2011
A Hazard Analysis and Critical Control Point (HACCP) Program or the National Poultry Improvement Plan	77	78
Specific animal welfare requirements, such as space per bird, or the Humane Farm Animal Care certification	90	94
At least one barn with evaporative cooling	77	88
At least one barn with tunnel ventilation	79	90
Beef feedlots		
Percentage of large** feedlots....	1999	2011
Applying individual-animal identification	40	53
With operators that perceived that respiratory vaccines given at weaning were very or extremely important	51	80

*An animal unit is a way to normalize across ages of hogs; roughly, it translates to 1,000 pounds of live weight.

**“Large feedlots” refers to those with a capacity of 1,000 head or more.

Sources: Hogs: USDA, Economic Research Service (ERS) calculations from the 2009 and 2015 Agricultural Resource Management Surveys on Hogs. Broilers: ERS calculations from the 2006 and 2011 Agricultural Resource Management Surveys on Broilers. Beef feedlots: USDA, Animal and Plant Health Inspection Service, 2013a, 2013b, and 2013c.

²¹These are the most recent years for which data are available.

Because beef production is less vertically integrated than the broiler and hog sectors, with multiple agents deciding on practices through an animal's life, it is more challenging to assess the industry's practices succinctly. Table 4 shows the prevalence of one practice adopted on large-scale feedlots that may lessen antibiotics use as well as feedlot operators' opinion of the effectiveness of another such practice that happens before cattle reach feedlots. Individual-level identification can enable the sorting of animals by their place of origin, prior vaccinations, and prior disease treatment. It can also assist in separating diseased cattle from others, potentially reducing the spread of disease. Additionally, feedlot operators increasingly viewed the administration of respiratory vaccines prior to arrival at the feedlot as very or extremely important.

These statistics are all drawn from years prior to the recent FDA guidances, suggesting they are driven by something other than regulation. The increasing adoption of such practices suggests that demand for antibiotics may decline.

On the other hand, disease pressures may intensify, driving up demand for antibiotics. The emergence and spread of new bacterial strains that may threaten human and animal health have implications both for foodborne disease and for future antibiotics use in food animals. The prevalence of many livestock diseases has been reduced during the last century as technology, biosecurity, and sanitation have improved in global livestock production. However, at the same time, major unexpected disease challenges have emerged. Rapid intensification of livestock production in industrializing nations such as Brazil and China and increasing global trade in livestock products will present new challenges. For example, Perry et al. (2013) suggest that growth in livestock production near urban areas in countries in South America and Asia will create "hot spots" of animal health risk and that the movement of people and animals in an increasingly globalized world can also affect animal disease dynamics.

Antibiotic resistance that is clinically and economically relevant for livestock production may also affect future demand for antibiotics use. One example of an endemic disease where resistance might affect demand for antibiotics use is bovine respiratory disease (BRD) in cattle. BRD is a common respiratory infection in cattle that can be caused by several different types of bacteria (Lubbers and Hanzlicek, 2013). BRD is the most common cause of death of cattle in U.S. feedlots, and the annual economic losses are estimated to be close to \$1 billion (Loneragan et al., 2001; Lubbers and Hanzlicek, 2013).

There is evidence that mortality rates from BRD may be increasing over time (Loneragan et al., 2001; USDA, APHIS 2011; Engler et al., 2014). Though many factors contribute to increased BRD mortality rates, research suggests that several BRD pathogens are becoming more resistant to antibiotics over time (Lubbers and Hanzlicek, 2013; DeDonder and Apley, 2015). Ongoing research examines how to quickly and accurately test BRD pathogens for antimicrobial susceptibility before treatment. Because of the economic consequences of BRD and the evidence of increasing resistance, beef producers may need to use more or newer antibiotics to treat BRD in the future.

Changing Demand for Meat Means Changing Demand for Antibiotics

Even if regulations and consumer preferences decrease the amount of antibiotics used per animal in the United States and EU, the amount of antibiotics sold could still conceivably increase if the number of animals in these regions increase. Behind China, the United States and EU constitute the

largest producers of meat in the world. In 2015, the EU supplied 14.7 percent of global meat, while the United States produced 13.4 percent (China produced 26.9 percent).

Production of meat in the United States is predicted to continuously increase but at a slowing pace. Between 1990 and 2000, domestic production grew 33 percent, but between 2000 and 2010, it grew only 12 percent. Since 2010, production has continued to grow, but annual growth rates are lower than in prior decades. In the EU, the production growth *rate* has risen, even as production growth has continued lower than in the United States. Between 2000 and 2009, EU meat production grew only 1 percent, and between 2010 and 2016, it grew 7 percent.²²

Production of food-animal products in the United States and EU (and, therefore, sales of antibiotics to these regions) will depend on both domestic and foreign demand. Domestic *consumption* in the United States and EU is growing but less quickly than production. U.S. domestic consumption of domestically produced meat grew 22 percent between 1990 and 2000 and grew only 7 percent between 2000 and 2010—sluggishness due to slowly rising populations and relatively flat consumption per capita (U.S. Census Bureau, 2014). The situation in the EU is similar. Instead, a growing share of U.S. and EU production is exported.²³ Sales of antibiotics in the United States and EU will be partly driven by demand for food-animal products in other regions.

In 2015, the United States and Brazil tied as the world's largest exporters of beef, pork, and poultry products, each constituting 20.4 percent of all global meat exports. The largest export destinations (by value) for U.S. meat and poultry products are in Asia, other countries in North America, and South America.²⁴ The EU is the world's third largest exporter of meat products at 12.7 percent.²⁵ Similar to the United States, many of the EU's top export destinations for meat and poultry products are in Asia. China is the number one destination for EU meat products (by value), followed by Japan.²⁶ The major export destinations for U.S. and EU meat products are largely predicted to continue growing. Chinese meat imports have been increasing rapidly, and the country is predicted to be a continued source for market opportunities (Gale, 2015).

Trade *agreements* reduce tariff and non-tariff barriers to trade, and as such, can contribute to increased demand for U.S. meat and poultry exports. In contrast, trade *restrictions* may reduce export demand (and by extension, sales of antibiotics). These barriers to trade can be sanitary and phytosanitary measures, as well as border measures such as tariffs and quotas (Lively, 2013).

Although U.S. and EU livestock production are important drivers in antibiotics sales and development, they are not the entire market. Particularly important markets for antibiotics are the low- and middle-income countries with rapidly rising food-animal production (see box “Increasing Production of Food Animals in Low- and Middle-Income Countries and What It Means for Antibiotics Sales and Animal Health Product Development”). Although these countries, particularly China, are predicted to increase their use of antibiotics in food-animal production, they are also risky sources of revenue because of insecure intellectual property rights, national drug pricing schemes, competition from counterfeit drugs, and uncertain approval processes.

²²All statistics in this paragraph were calculated from data from OECD-FAO Agricultural Outlook (2017).

²³Calculations were made from OECD-FAO Agricultural Outlook data (2017).

²⁴Calculations were made from U.S. Census Bureau USA Trade Online data (2017).

²⁵Calculations were made from OECD-FAO Agricultural Outlook data (2017).

²⁶Calculations were made from Eurostat database.

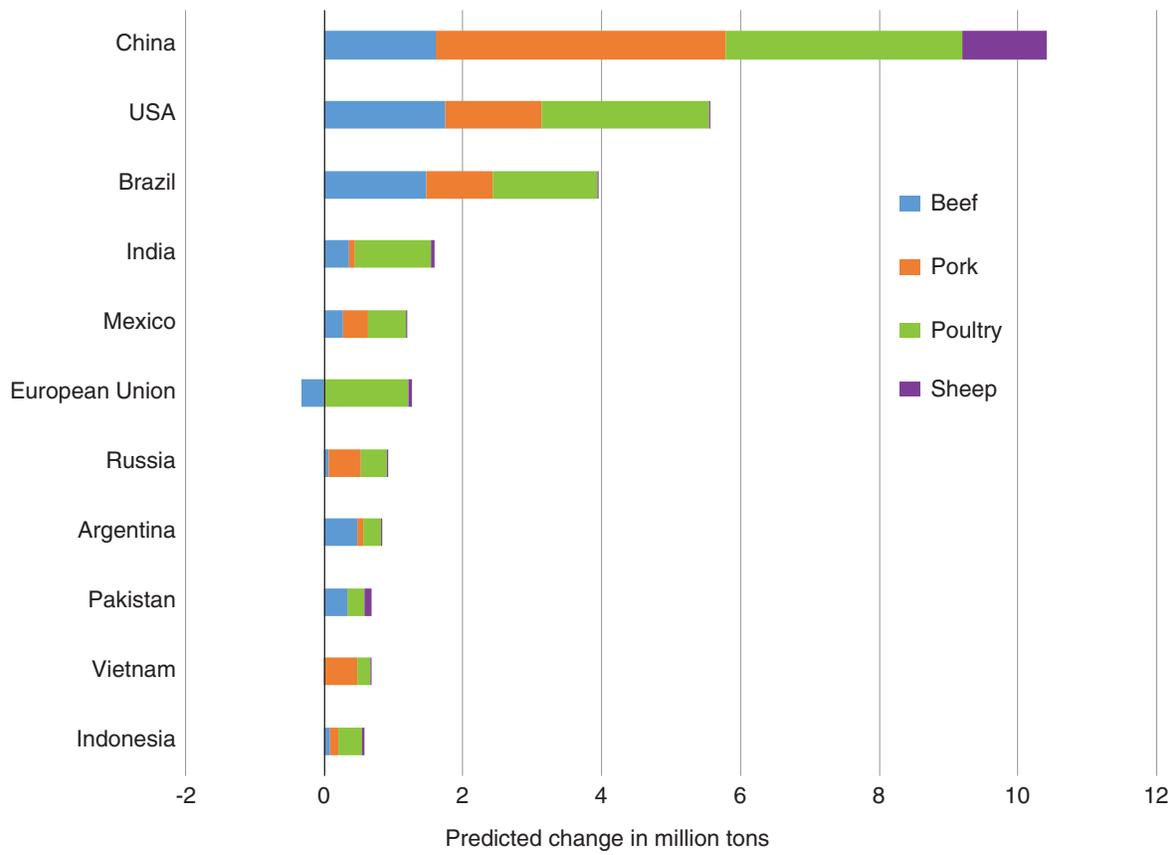
Increasing Production of Food Animals in Low- and Middle-Income Countries and What It Means for Antibiotics Sales and Animal Health Product Development

Demand for food-animal products is rapidly increasing in certain countries, leading to changes in meat production practices. Meat production in China, Brazil, and India is high and rapidly growing (fig. 5). Other, smaller countries like Vietnam and Pakistan also have rapidly growing meat production, although they are starting from lower volumes. This growth accompanies a shift from subsistence to commercial production, with increasing levels of animal concentration, production modernization, and antibiotics use. Although few data on antibiotics use in food-animal production are available in these countries, estimates suggest that China, Brazil, India will be the first, third, and fourth largest users of food-animal antibiotics by 2030, respectively. (The United States is predicted to be the second.) By 2030, China is predicted to use over 10 times more antibiotics for food production than the United States (Van Boeckel et al., 2017).

Animal pharma's reaction to this increased demand for antibiotics for food-animal production is complicated by the institutions (or lack thereof) in many of these countries. Countries have different regulatory approval processes for drug and biologic products, often with requirements for local testing. Some countries have greater formal intellectual property protections than others, and enforcement of these rules varies in countries. State-level interventions in businesses and drug pricing may also create barriers to entering these markets. Further, producers in these regions may seek very low-cost drug interventions, so animal pharma producers may not find it cost-beneficial to develop products for these markets, as newer products are likely to be more expensive. However, despite these barriers, animal pharma company reports suggest that the major firms have been entering these newer markets (e.g., Gerecke, 2005; Heifetz, 2014; Zoetis, 2013; Boehringer-Ingelheim, 2016), but not without problems (Weintraub, 2016).

Figure 5

Countries with the largest predicted changes in meat production, 2015-25



Source: USDA, Economic Research Service calculations from United Nations, Food and Agriculture Organization, OECD-FAO Agricultural Outlook 2016 data.

Trends in Sales of Antibiotics for Livestock Production

The current status and future prospects of antibiotics sales in the United States and EU are important not only for the animal pharmaceutical sector but also for livestock producers, advocacy groups, and government agencies.

U.S. Antibiotics Sales Quantities for Use in Food-Animal Production

Publicly available data for total U.S. sales of antibiotics for use in food-producing animals began in 2009 under the 2008 Amendments to the FDA's Animal Drug User Fee Act (ADUFA). These data show the quantity of antibiotics sold by weight of active product; this measure is not ideal for estimating all facets of antibiotics use in livestock production, but it is the only measure provided in the sales data.²⁷

The most recent 2 years of released data (2016 and 2017) show marked drops in sales compared to the prior years. FDA reports that domestic sales of antibiotics for use in food-producing animals rose from 12.6 million kilograms (kg) in 2009 to 15.6 million kg in 2015, before dropping to 14.0 million kg in 2016 and then to 11.0 million kg in 2017 (fig. 6). The 24-percent increase between 2009 and 2015 (with an annual growth between 1 and 8 percent) changed to a 10-percent decline between 2015 and 2016 and a 22-percent decline between 2016 and 2017 (fig. 7).²⁸

FDA also reports sales in terms of medical importance to human disease treatment²⁹; between 2009 and 2016, the share of antibiotics sold for food-animal production in the United States that were “not currently medically important” remained fairly constant at about 39 percent. The drop in sales in 2017 led to not-currently-medically-important antibiotics comprising 49 percent of sales in that year. The largest share of medically important antibiotics sold was tetracyclines (comprising an average 41 percent of all antibiotics sold, or 69 percent of medically important antibiotics sold). Both medically important and non-medically important products saw declining sales between 2015 and 2017, although the medically important drop was larger (43 percent) than the non-medically important (9 percent).

The 2016 and 2017 drops in U.S. antibiotics sales for food-animal production cannot be explained by similar drops in the livestock products produced. Although, from 2009 to 2015, sales of antibiotics for food-animal production generally outpaced the growth in meat and milk produced (fig. 7), the dive in antibiotics sales in 2016 and 2017 is not paralleled by a similar drop in meat or milk produced.³⁰

²⁷For example, sales by weight does not provide the number of doses provided. Additionally, antibiotics sales are for products used in food-producing animals. These products might have labels that also allow for their use in companion animals. However, FDA notes that in 2016, only 13 of 132 actively marketed, medically important antibiotics for use in food-producing animals also were approved for use in companion animals. FDA also notes that these 13 drugs account for less than 2 percent of overall sales, concluding “The use of these thirteen drug products in companion animal[s] likely has little to no effect on trends in the overall reported sales of antimicrobial drugs” (U.S. FDA, 2017b).

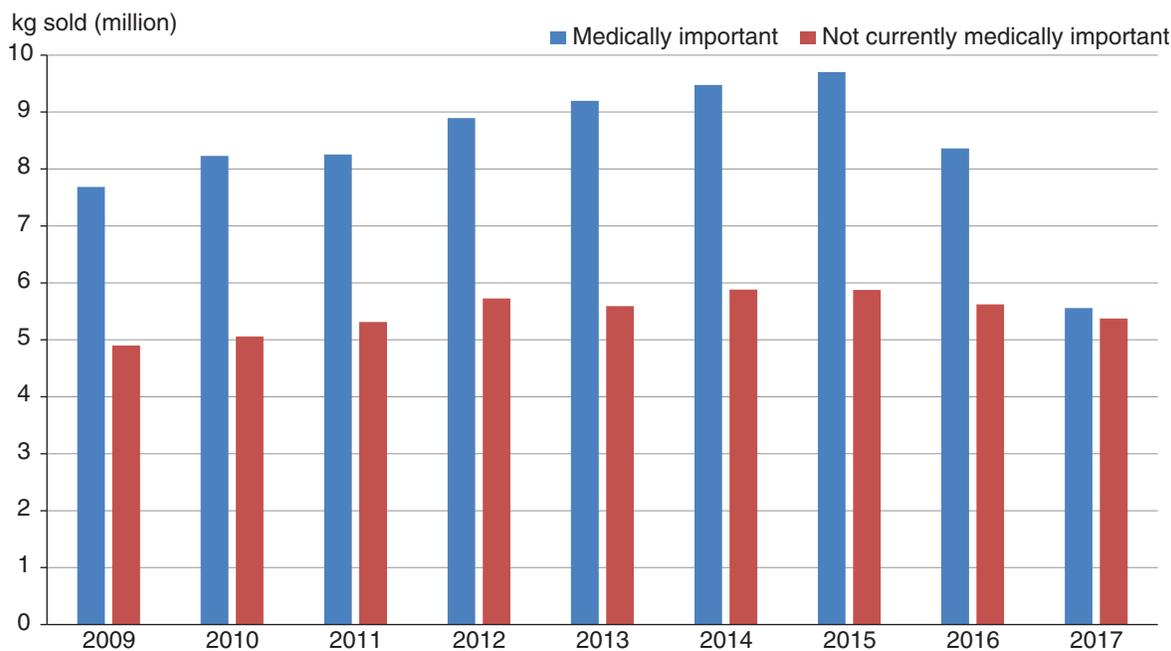
²⁸Exports of antibiotics constituted only 1.6 percent of overall sales in 2009—a share that, by 2016, had been reduced 97 percent to 0.05 percent of overall U.S. sales (U.S. FDA, 2017c).

²⁹Broadly, “medically important” means that the antibiotic is in a class of antibiotics important for disease treatment in humans. FDA outlines the antibiotic classes it considers to be medically important in Appendix A of Guidance for Industry #152. A concise listing of currently marketed drug classes not considered to be medically important is also provided in table 1 of the *Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* (U.S. FDA, 2017b).

³⁰Plotting animals in inventory (not shown) also reveals (1) that growth in antibiotics sales outpaced the growth in animals in inventory and (2) the growth in animals in inventory did not drop in 2016 or 2017.

Figure 6

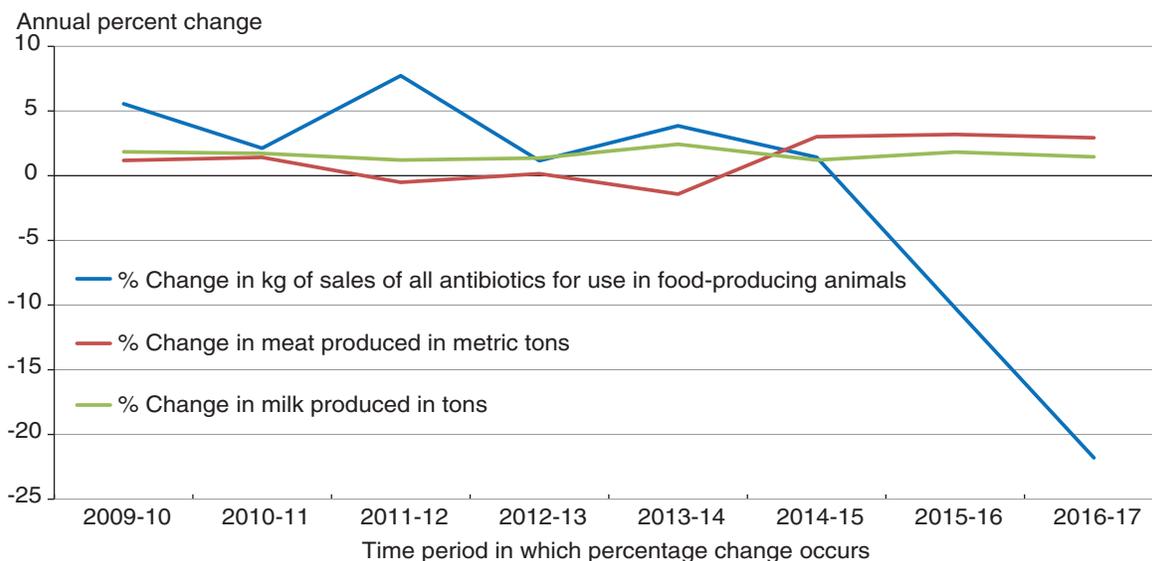
Sales of antibiotics for use in food-producing animals in the United States, by medical importance, 2009-17



Source: USDA, Economic Research Service calculations from U.S. Food and Drug Administration, 2018d. Unit is in million kilograms (kg) of active ingredients sold. Domestic sales only.

Figure 7

Annual percentage changes in all antibiotics sold for use in U.S. food-producing animals, meat produced, and milk produced



Sources: USDA, Economic Research Service calculations from U.S. Food and Drug Administration Animal Drug User Fee Act data (U.S. FDA, 2018d) and United Nations, Food and Agriculture Organization, OECD-FAO data on domestic production. "Meat" is the sum of beef, pork, chicken, and sheep (in metric tons) produced for food. Beef, pork, and sheep are measured in terms of carcass-weight equivalents. Chicken is measured in terms of ready-to-eat weight. Antibiotics sales are domestic sales only.

What can explain this large drop in antibiotics sales in 2016 and 2017? FDA’s new regulations on the use of antibiotics for production purposes (see subchapter “U.S. and EU Regulations on Use of Antibiotics in Food-Animal Production”) were announced in 2013 but not fully implemented until January 2017. Hence part of the drop in 2016 may be a result of producers’ and drug suppliers’ compliance with the regulations before they fully took effect. The even larger drop in 2017 is likely due in part to the institution of the FDA policies. Another reason for the drop is likely due to a large share of broiler production moving to “raised without antibiotics.” (See “Changes in Consumer Preferences for Meat and Poultry Products Raised Without Antibiotics,” on page 18.)

Sales of Food-Animal Antibiotics in Select EU Countries

Multiple countries in Europe collect data on antibiotics sales for food-animal production. Also, the European Medicines Agency (EMA) has a measure called a population correction unit (PCU), which provides an estimate of the total size of the food-producing animal population in the country.³¹ Dividing the amount of antibiotics sold by the PCU provides a measure of the use per animal, which in turn reveals whether changes in total sales are due to changes in livestock produced, or in intensity of use.

Although the European Medicines Data collected data from 30 countries in 2015 (the most recent year of data), only 17 countries have consistent data for 2010 to 2015 (table 5). These 17 countries show a 31-percent decline in antibiotics sales over the time period, with only a 0.24-percent decline in animal biomass produced. Thus, antibiotics sales per animal biomass produced also declined by 30 percent. Of the 30 countries reporting data to the EMA in 2014 and 2015, 21 had reduced or constant sales of antibiotics over that time period.

Table 5

Sales of antibiotics and total animal biomass produced in European countries, 2010-15

	17 countries with data for 2010-15							All 30 countries	EU-28*
	2010	2011	2012	2013	2014	2015	% change, 2010-15	2015	
Sales (million kg)	4.47	3.87	3.71	3.40	3.47	3.10	-31%	8.30	8.25
PCU (million kg)	31,565	31,907	31,560	31,230	31,117	31,491	-0.24%	61,266	58,421
Sales/PCU (mg/kg)	141.53	121.15	117.49	108.96	111.61	98.59	-30%	135.46	141.24

Note: PCU = Population correction unit. kg = kilogram. mg = milligram.

Source: European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) database (2017). The 17 countries with data for 2010-2015 are Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Iceland, Ireland, Italy, Latvia, Norway, Portugal, Slovenia, Sweden, and United Kingdom. The additional 13 reporting countries in 2015 are Bulgaria, Croatia, Cyprus, Germany, Greece, Lithuania, Luxembourg, Netherlands, Poland, Romania, Slovakia, Spain, and Switzerland. *The EU-28 includes all 30 countries reported minus Iceland, Norway, and Switzerland. The EU-28 also includes Malta, but Malta did not report antibiotics sales.

³¹A comparable PCU number is being developed by FDA for the United States (U.S. FDA, 2017d), but is not yet released; hence, no comparison to the U.S. is available at this time.

The EMA numbers are a useful indicator of trends in antibiotics sales, particularly as certain EU countries have more stringent regulations on antibiotics use than the United States does.³² (See “U.S. and EU Regulations on Use of Antibiotics in Food-Animal Production,” on page 17.) However, without data prior to 2006, it is hard to attribute sales trends to an effect of the regulations.

Impact of Regulations on Antibiotics Sales in Select EU Countries

Several EU countries adopted early regulations on antibiotics use in livestock production, even before the EU-wide ban on growth-promoting antibiotics in 2006. Three such countries that have significant meat production and consistent data on antibiotics sales are Denmark, the Netherlands, and Sweden. Here we explore trends in these countries’ sales of antibiotics for food animals after the initiation of these countries’ specific regulations. Each of these countries have national monitoring systems for antibiotics sales, but not all countries have data available for the same years.

Denmark

Denmark is a major European pork-producing country and, like the United States, employs confinement feeding. In Denmark, total antibiotics use for growth promotion and therapeutic purposes peaked in 1994. Between 1994 and 1999, restrictions on the use of certain antibiotics for growth promotion and voluntary removal of growth promoting antibiotics by industry led to a sharp decrease in total antibiotics sales volumes (see fig. 8). An end of antibiotics use for growth promotion in 1999 was followed by an increase in therapeutic use of antibiotics in young pigs, but total sales dropped again following the 2010 “yellow card initiative.” Under this initiative, veterinarians and farmers are warned when antibiotics use per animal exceeds a certain threshold, triggering additional restrictions and veterinary surveillance (DANMAP, 2016; U.S. Government Accountability Office, 2011).

The Netherlands

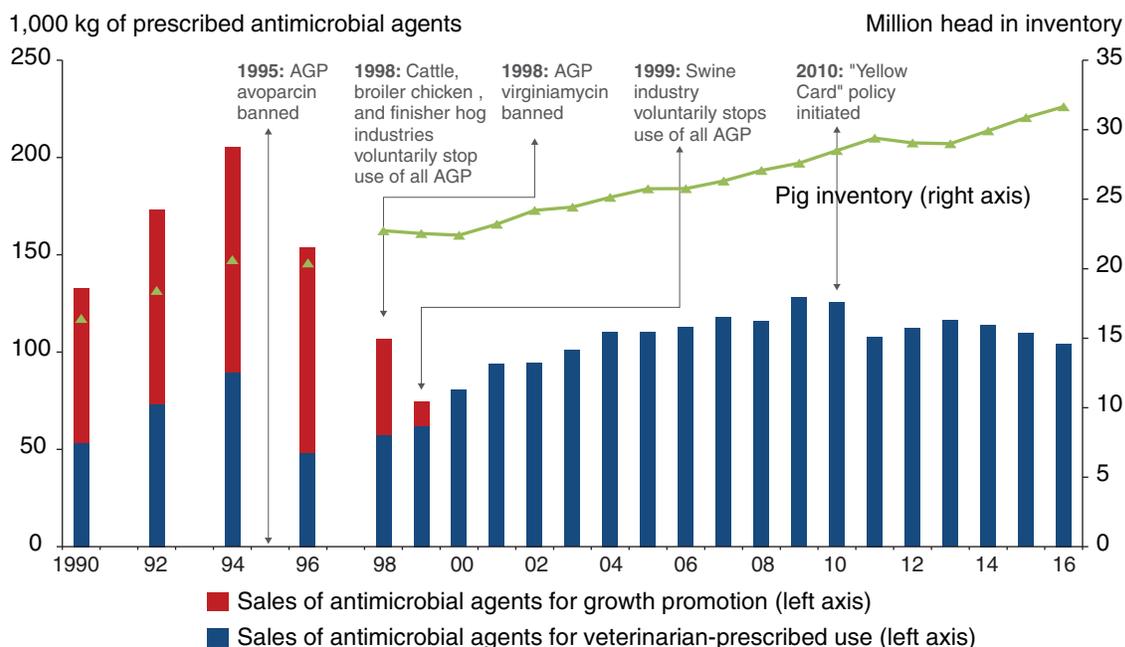
The Netherlands are also a major European pork producer employing livestock production like that seen in the United States. Livestock antibiotics use in the Netherlands more than doubled between 1990 and 2007, from 275,000 kg to 600,000 kg (Speksnijder et al., 2014).³³ In the years preceding the 2006 EU-wide ban on growth promoters, the Netherlands had already been decreasing its antibiotics use such that, when the ban took place, growth-promotion uses were already at zero (fig. 9). In 2009, the Netherlands adopted a national requirement to halve antibiotics use by 2013, which it accomplished through increased veterinary oversight and use monitoring. As a result, total livestock antibiotics use in the Netherlands declined by 58 percent between 2009 and 2013. Although the reduction in growth promoters correlates with a downward trend in pigmeat production between 1999 and 2003, the marked decrease in antibiotics use between 2009 and 2015 does not accompany a reduction in pork production.

³²Notably, because Europe considers ionophores to be coccidiostat feed additives, not antibiotics, the total numbers are not directly comparable. However, U.S. and EU totals of medically important antibiotics can be more accurately compared (European Medicines Agency, 2017).

³³Despite this statistic, we were not able to locate data for 1991 to 1998 on antibiotics sales in the Netherlands. Further, we do not have information on what portion of these sales in 1990 were for growth promotion versus therapeutic applications.

Figure 8

Sales of antimicrobial agents in all types of animals in Denmark and pig inventory, 1990-2016, with dates of policies

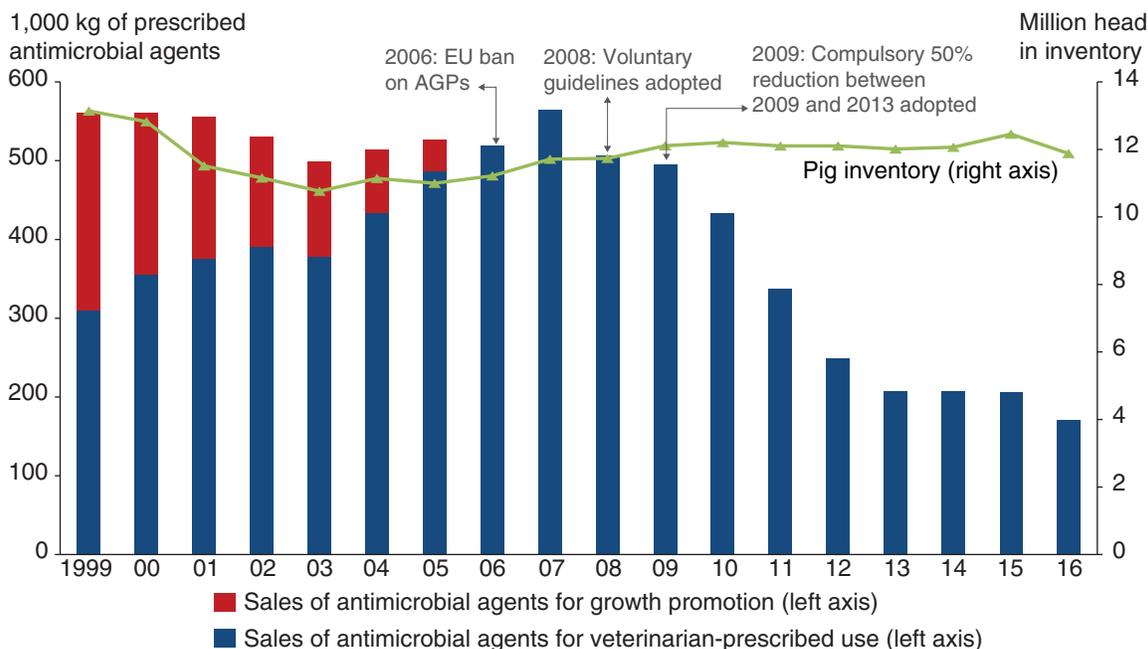


Note: AGP = “antimicrobial growth promoter.” The European Union (of which Denmark is a member) banned growth-promotion uses of antibiotics in 2006. Because Denmark had already taken this action in 1999, EU policy date is not shown.

Sources: DANMAP (1999 and 2010, 2011, 2012, 2013, 2014, 2015, and 2016). Data on antimicrobial amounts and pig inventory was not reported by DANMAP for 1991, 1993, 1995, and 1997.

Figure 9

Sales of antimicrobial agents in all types of animals in the Netherlands and pig inventory, 1999-2016, with dates of policies



Note: kg = kilogram. AGP = antimicrobial growth promoter.

Sources: Wageningen UR (2010, 2011). SDa Autoriteit (2012, 2013, 2014, 2015, 2015, 2016). Pork inventory data come from Eurostat’s online database.

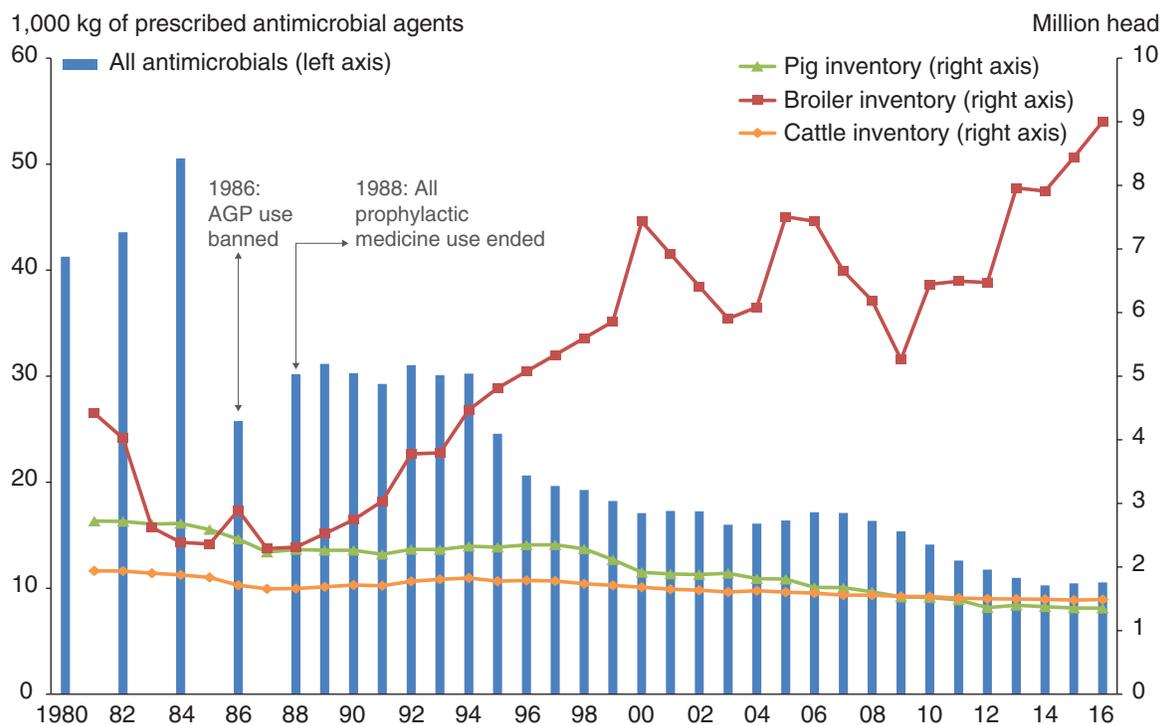
Sweden

Sweden banned the use of antibiotics in livestock for growth promotion in 1986, and sales of antibiotics fell from 50,000 kg of active substance in 1984 to 30,000 kg by 1988 (fig. 10). Grave and co-authors (2006) report that approximately 20,000 kg of antimicrobials were used for growth promotion in 1984, which declined to no use in 1988. In the first 2 years after the ban, prescription in-feed antibiotics were provided to broilers to prevent disease outbreaks (Grave et al., 2006). This led to a slight increase from 1986 to 1988 in antibiotics sales, such that therapeutic sales in 1984 and 1988 were similar. Sweden was able to alter management practices to reduce antibiotics use, and by 1995 antibiotics sales began to decline. Although pig production gradually declined in Sweden between 1986 and 2016, the number of poultry in inventory has more than tripled.

The experiences from Denmark and Sweden suggest that bans on use of antibiotics for growth promotion were accompanied by drops in antibiotics sales. Denmark's further steps to curb antibiotics use in agriculture in the form of the "yellow card" initiative did appear to reduce antibiotics sales or at least stop their upward trend. The Netherlands did not have a ban on antibiotics for growth promotion until the EU-wide policy in 2006, although growth-promotion uses had declined to zero leading up to the ban. The Netherlands' compulsory reduction in 2009 was definitely accompanied by a drop in antibiotics sales. Together, these experiences suggest that policies do affect antibiotics sales.

Figure 10

Sales of antimicrobial agents in all types of animals in Sweden and pig, broiler, and cattle inventories, 1980-2016, with dates of country-specific policies



Note: kg = kilogram. AGP = antimicrobial growth promoter.

Sources: Antimicrobial sales data from Statens Veterinärmedicinska Anstalt (SVA) National Veterinary Institute Swedres/Svarm reports, 2000-17, and Government Offices of Sweden, 1997. No statistics exist for antimicrobials for 1981, 1983, 1985, or 1987. No statistics for antimicrobial agents used for growth promotion versus those used for therapy are available. Livestock statistics for 1981-2007 are from the Statistics Sweden database; data from 2008-2016 are from the Swedish Board of Agriculture. No national data for poultry inventory are available for 1996-1998 and 2001-2002, so the statistics for these years are linear extrapolations.

Quantity May Not Fully Capture Sales Revenues of Antibiotics

Gross revenues will be a function not only of quantities sold but also of price. The cases of Denmark, the Netherlands, and Sweden suggest declines in overall sales of antibiotics, but the data may not provide the overall effect on revenues (price multiplied by quantity). Economic theory predicts that as demand for a product falls, both quantities and prices will decline, leading to overall declines in revenues. Falling sales of antibiotics (by weight) might not fully capture the effect on industry revenues due to potential shifts in the composition of antibiotics sold. The drop in antibiotics sales may be due to livestock producers replacing high quantities of older, cheaper generic drugs traditionally used in feed with more expensive narrow-spectrum antibiotics targeted at high-value treatments. Although this transition may result in declining overall quantities of antibiotics sold, it may not have a large effect on overall revenues of animal pharma firms.

A more nuanced exploration of the specific antibiotics used is difficult because of a general lack of publicly available data, but it may be possible by piecing together different data sources or gaining access to proprietary sales data. Such an approach would be necessary for understanding how producers have reacted to regulations and market trends and would provide better indications of what choices producers make to reduce antibiotics use. This approach would also provide a better picture of how these possible changes in sales may affect overall revenues.

Antibiotic products are dispersed through a number of channels and vendors, making it difficult to assess prices. First, many antibiotics are only available via veterinarians, and even when no veterinarian prescription is required, veterinarians may be still be the ones distributing drugs. Veterinarians may work for meat production companies (integrators or feedlots); in these settings, they may be able to command volume pricing for antibiotics. Veterinarians may also be in individual practice and be able to capture discounts for multiple products. Finally, antibiotics are sold over the counter to individual buyers via wholesalers or retailers. Each of these types of buyers might see different prices for the same drug; hence, it is difficult to calculate total revenues by multiplying quantities by prices.

No time series statistics on revenues from antibiotics sales are publicly available. The closest data we have is a reported measure of \$5 billion in global revenues from antibiotics in 2017 (Watt, 2018, reporting a statistic from the industry group Animal Pharm). With respect to measures over time, animal pharma's overall reported global sales (including antibiotics, biologics, and medicinal feed additives) increased in 2016 (HealthforAnimals, 2018). This increase suggests that the drop in antibiotics sales volumes in the United States did not have a pronounced impact on global animal pharma revenues overall.

The Animal Pharmaceutical Industry’s Development of Veterinary Products

As described previously, the long, complex, and costly research and development processes for new drugs mean that animal pharmaceutical companies must choose wisely where to invest. Increasing medical attention to companion animals over the last several decades and the ability to market generic products, starting in 1988, create new market opportunities. Further, connections between the research processes of human and animal pharma mean that changes in human pharmaceuticals—especially those related to antibiotic development—likely affect what happens in animal pharma. Regulations on antibiotics pertinent to human medicine may dissuade animal pharma companies from investing to bring these products to market.

R&D Spending Increases While New Product Approvals Decline

In this subchapter, we examine research and development (R&D) spending by animal pharma and the trends in the numbers and types of products brought through regulatory approval.

The amount U.S.-based animal pharma has spent on R&D has increased from approximately \$604 million in 1989 to \$1.1 billion in 2017,³⁴ with a growth rate of 2.7 percent per year. Also, Fuglie and coauthors (2011) note that, between 1993 and 2010, the global research intensity in the industry (measured as the dollars spent on R&D divided by overall sales) remained fairly steady at about 8.6 percent. A recent report from the Animal Health Institute (the U.S. animal pharma industry trade group) also reflects an R&D intensity of 8.5 percent (Pham and Donovan, 2018). For comparison, R&D’s share of gross domestic product (GDP) was 2.7 percent in 2015 (National Science Foundation, 2018).³⁵

As total R&D spending increased, the total number of nongeneric drugs coming through the animal health R&D pipeline has declined (fig. 11). Because the number of products generated by the animal pharma industry greatly fluctuates from year to year, we show the 9-year moving averages of (1) the number of approved New Animal Drug Applications (NADAs), which exclude generics and (2) the number of new approved NADAs with an original ingredient. We define an “original” ingredient as one that has not been previously approved by itself or in combination. These provide two measures of innovation in drug research. The number of new pharmaceutical approvals excluding generics declined at an estimated 3.6 percent per year from 1989 to 2013. However, the number of “original” approvals remained relatively constant in this period.

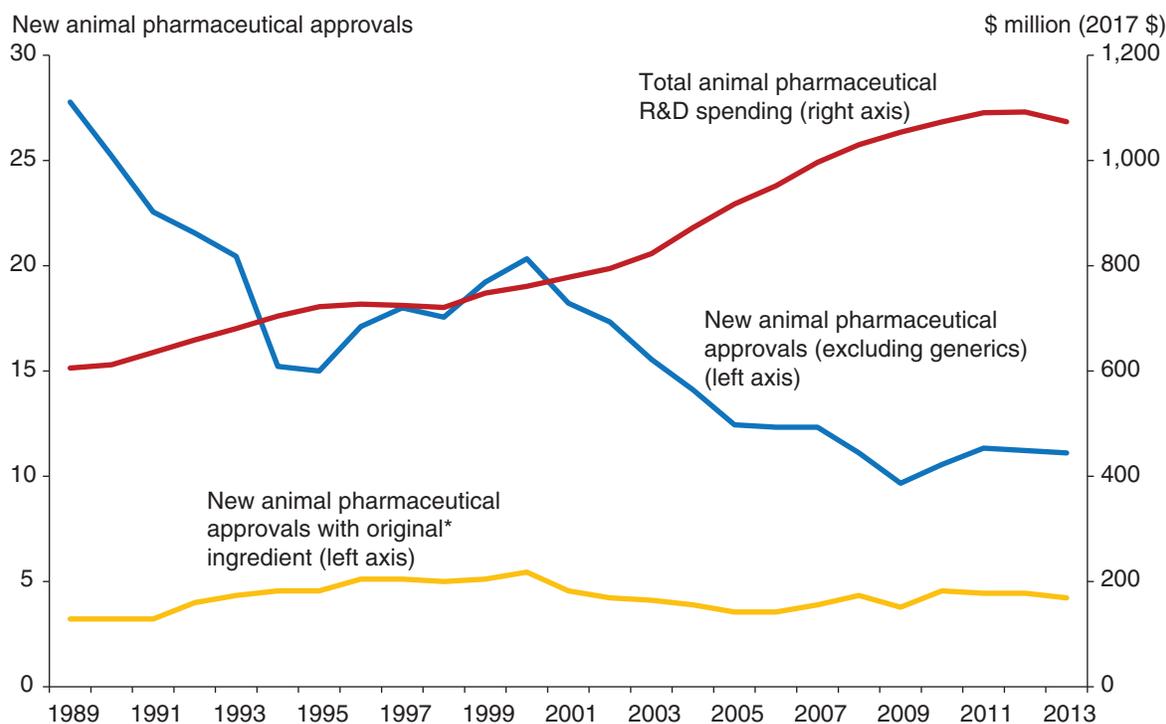
Given the increase in R&D spending and the declines in new products, it should not be surprising that the dollars spent per product is increasing (fig. 12). To examine the trend in R&D spent per new drug approved, we divide total R&D spending by the same measures of animal health product development as in figure 11. For all series, we examine 9-year moving averages where R&D is lagged by 5 years in relation to the number of approvals. (See Appendix for more description.) We adopted this approach to take into account the fluctuations in annual rates as well as the timelags between research spending and product approval. Notably, our approach captures R&D spending on drugs that failed to make it to approval.

³⁴Data received via personal communication with Keith Fuglie, USDA, Economic Research Service. Amounts expressed in 2017 real dollars; see Appendix for more data description.

³⁵In National Science Foundation (2018), see appendix table 4-1.

Figure 11

U.S. R&D spending on animal pharmaceuticals and numbers of new animal drug approvals, by type of approval, 9-year moving averages, 1989-2013



Note: * “Original” refers to chemical ingredients that have never been approved by themselves or in combination with other ingredients. Drug approvals do not include medical gases. In 2012, FDA updated the Food and Drug Administration Safety and Innovation Act (FDASIA) such that there were 62 approvals in 2015 for medical gases. R&D = research and development.

Sources: USDA, Economic Research Service (ERS) calculations using data received via personal communication with Keith Fuglie, USDA, Economic Research Service. Animal health R&D spending for U.S. firms, both domestically and abroad, on food and companion animals is expressed in real 2017 dollars. Converted from nominal dollars using the Bureau of Economic Analysis’s Biomedical Research and Development Price Index (BRDPI). A 9-year-moving average is estimated by averaging the values for 4 years prior to the year in question, the 4 years after the year in question, and the year in question. For this figure, we utilize data from 1985 to 2017 and calculate 9-year moving averages for 1989 to 2013. Drug approvals: ERS calculations using Food and Drug Administration (FDA) Green Books. See Appendix for further information on data.

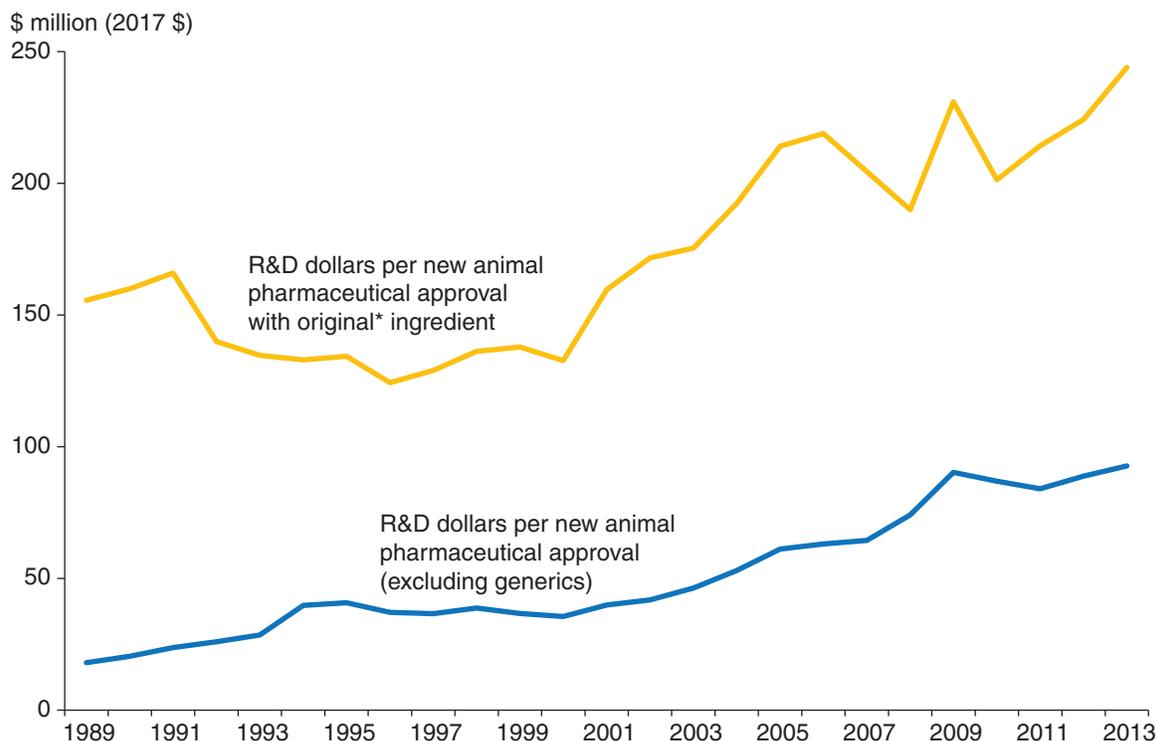
Figure 12 shows that the dollars per new animal drug trended upward from 1989 to 2013, regardless of the level of innovation in question. Exponential trends fitted through the series suggest that the R&D per new nongeneric drug approval increased at about 6.3 percent per year and spending per new “original” drug increased at 2.4 percent per year.

R&D dollars per new nongeneric drug approval averaged \$51 million in the period. If only drugs with an original ingredient are considered, the figure is \$173 million per drug (2017 real dollars). Figure 12 represents an upper bound on R&D spending per new animal product (where products include both drugs and biologics), as we do not include biologics. Combining pharmaceutical and biologic products in a single approval number is inappropriate because of different regulatory processes and scientific methods.³⁶

³⁶We do not show the trend in the number of veterinary biologic licenses over time, as our goal is to examine changes in innovation. Instead of being “approved,” biologics are “licensed.” APHIS CVB grants licenses to a firm for an individual biologic product. However, that product may be updated over time, without the license number changing. Hence, the number of licenses is not a good indication of innovation in the field of veterinary biologics. Additionally, a new license number is provided if a firm sells its product to a different firm and the new firm continues to manufacture the products.

Figure 12

R&D spending per new animal drug approval, 1989-2013, by type of new animal drug approval, lagged 9-year moving averages



Notes: Calculated as centered 9-year moving average of real R&D divided by 9-year moving average of approvals, lagged 5 years. For this figure, we use R&D data from 1980 to 2012 and drug approval data from 1985 to 2017. See Appendix for description of methodology. All values are in real 2017 dollars. Converted from nominal dollars using the Bureau of Economic Analysis's Biomedical Research and Development Price Index (BRDPI). R&D = research and development.

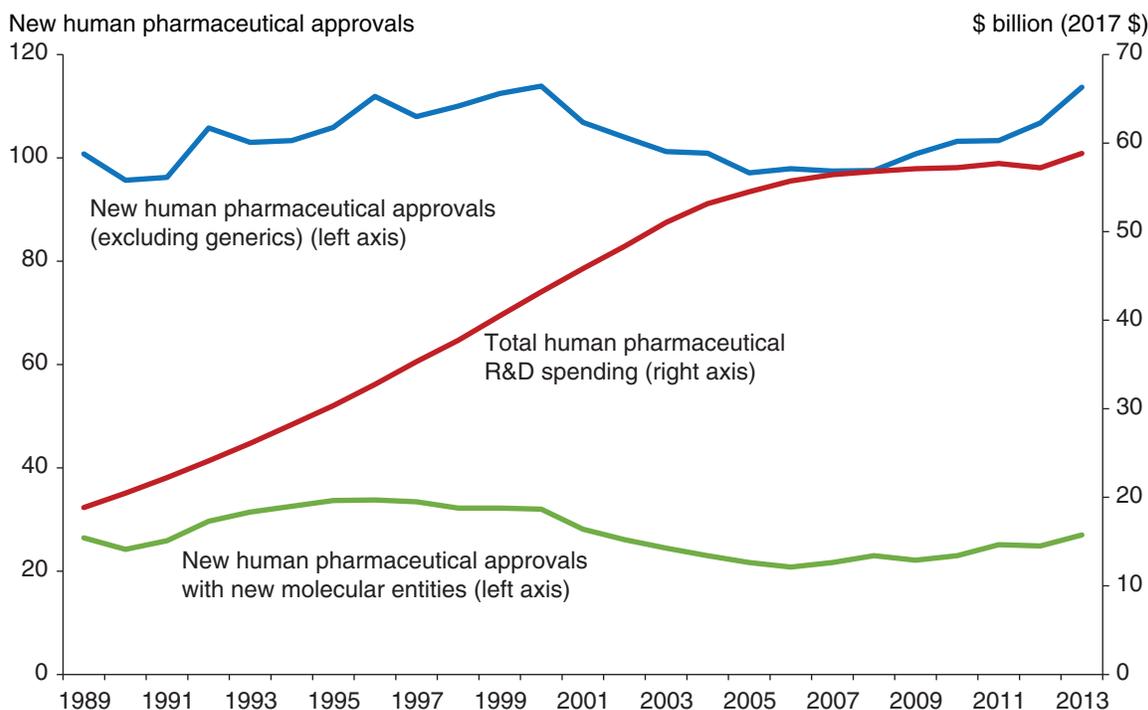
Sources: USDA, Economic Research Service calculations from Food and Drug Administration Green Books (New Animal Drug Applications), data received via personal communication with Keith Fuglie, USDA, Economic Research Service (animal health R&D spending for U.S. firms both domestically and abroad, on food and companion animals). See Appendix for more data description.

Examination of similar measures for human drugs and pharmaceutical R&D can help us assess whether R&D spending on animal drugs is trending differently from human drugs. If trends in human and animal pharmaceutical development parallel each other, this finding would suggest they share a common driver. Fig. 13 shows the total R&D spending for human pharma products. R&D spending increased from \$18 billion in 1989 to \$71 billion in 2017 (in 2017 real dollars), at approximately 4.9 percent per year in this time period (ERS calculations based on PhRMA (2018)).³⁷ Unlike the animal pharma market, human pharma R&D spending appears to level off in about 2005.

³⁷R&D data comes from the industry group, the Pharmaceutical Research and Manufacturers of America (PhRMA), which publishes series of R&D spending from its member companies. These numbers represent total R&D spending by US-owned PhRMA member companies either in domestic or foreign research departments.

Figure 13

U.S. R&D spending on human pharmaceuticals and number of new human drug approvals, by type of approval, 9-year moving averages, 1989-2013



Note: R&D = research and development.

Sources: R&D: USDA, Economic Research Service (ERS) calculations from PhRMA Industry Profile 2017 and 2013. For this figure, we utilize data from 1985 to 2017 and calculate 9-year moving averages for 1989 to 2013. Converted from nominal dollars using the Bureau of Economic Analysis’s Biomedical Research and Development Price Index (BRDPI). Drug approvals: ERS calculations from Food and Drug Administration Center for Drug Evaluation and Research data on drug approvals. See Appendix for more data description.

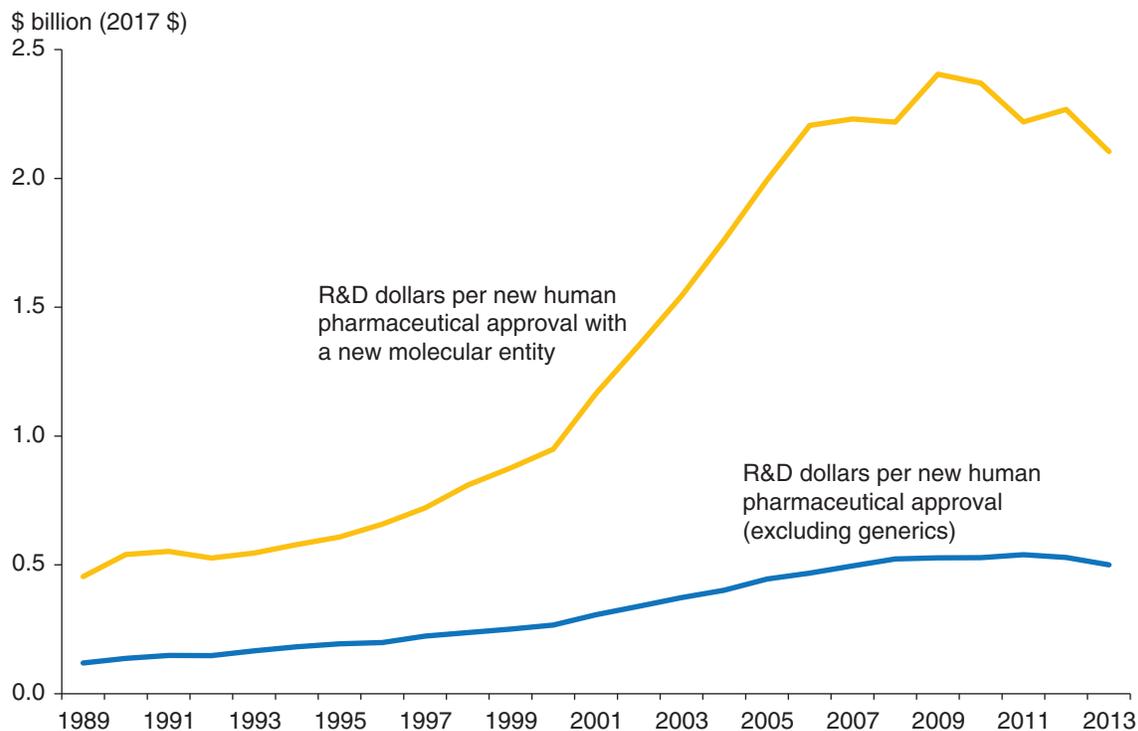
Figure 13 also shows similar pharma approval measures to those in figure 11, but for human pharmaceutical approvals. For human drugs we show two series, similar to those for animal health: (1) the number of new drug approvals by FDA’s Center for Drug Evaluation and Research (CDER), which are nongeneric “new drug approvals” (NDAs), and (2) the number of new drug approvals with a “new molecular entity” (NME). FDA describes new molecular entities as products that contain “active moieties that have not been approved by FDA previously” (U.S. FDA, 2018e). Similar to the animal health series, these represent two versions of innovation. Unlike animal pharma approvals, the number of new human drug approvals has remained relatively steady since 1989.

Figure 14 shows measures of R&D spending per new drug approval in the human pharma market (similar to what is shown for the animal pharma market in figure 12). In the human pharma market, R&D spending per drug also rose, although faster than the animal pharma market. R&D spending per new nongeneric human drug approval increased at approximately 6.8 percent per year between 1989 and 2018. R&D per drug approval with a new chemical entity rose at about 8.0 percent per year. In both series, R&D spending growth slowed around 2005, reflecting the overall slowdown in total R&D spending. In the period, the average amount spent per drug with a new chemical entity in the human pharma market was \$1.3 billion (2017 real dollars) and average spending for a new nongeneric was \$330 million.

Comparing the animal and human pharma series, we notice three things. First, the number of nongeneric drugs approved in the human market was nearly 6.6 times higher than the number of animal drugs approved between 1980 and 2017.³⁸ Second, the human health spending per new approval was 6.5 to 7.8 times higher than animal health spending.³⁹ Third, the increase in the dollars spent per new animal pharmaceutical product was echoed in the human pharma market. The rise in the amount spent for the more innovative drugs (the “originals” in animal pharma and the new molecular entities in human pharma) shows a more marked increase in the period—significantly more than spending for any nongeneric drug.

Figure 14

R&D spending per new human drug approval, 1989-2013, by type of new drug approval, lagged 9-year moving averages



Note: R&D = research and development.

Sources: R&D: USDA, Economic Research Service calculations from PhRMA Industry Profile 2017 and 2013. For this figure, we use R&D data from 1980 to 2012, and drug approval data from 1985 to 2017. Converted from nominal dollars using the Bureau of Economic Analysis’s Biomedical Research and Development Price Index (BRDPI). Drug approvals: ERS calculations from Food and Drug Administration Center for Drug Evaluation and Research data on drug approvals. See Appendix for more data description.

In human pharma, the increase in R&D spending per drug is attributed to increased failure rates in drug testing and increased regulatory burdens (DiMasi et al., 2016). We do not have similar insight for the increase in R&D spending for animal pharma. What our findings do suggest is that an increasing R&D spending per new product in human pharma is correlated with a similar increase in animal pharma. More broadly, Bloom et al. (2017) document rising costs per innovation across a

³⁸This is calculated as the number of approvals for the human market between 1980 and 2017, divided by the number of approvals for the animal market between 1985 and 2017.

³⁹These numbers are calculated as the lagged moving average of R&D per new non-generic approval for 1989 to 2013 for the human market divided by the lagged moving average of R&D per new non-generic approval for 1989 to 2013 for the animal market. The lower number (6.5) represents the ratio for all non-generic drugs, while the higher number (7.8) represents the number for original drugs or new molecular entities.

wide array of industries (including computer chips, new plant varieties, and firms in general), which may suggest economywide factors slowing innovation (for example, the exhaustion of “low-hanging fruit” among possible research projects).

As the amount of R&D spent on each product rises, pharmaceutical companies must choose products that make the most economic sense. Even as the amount of research dollars per product rises, the market has evolved to include new products. Veterinary pharma companies make profit-maximizing decisions whether to invest in food or companion animals, what types of food animals or of drugs to invest in, and whether to market generic or original products. Pressures from consumers and policymakers may also affect the number and type of antibiotics developed.

Companion Animal Products Constitute an Increasing Share of Veterinary Drug Approvals

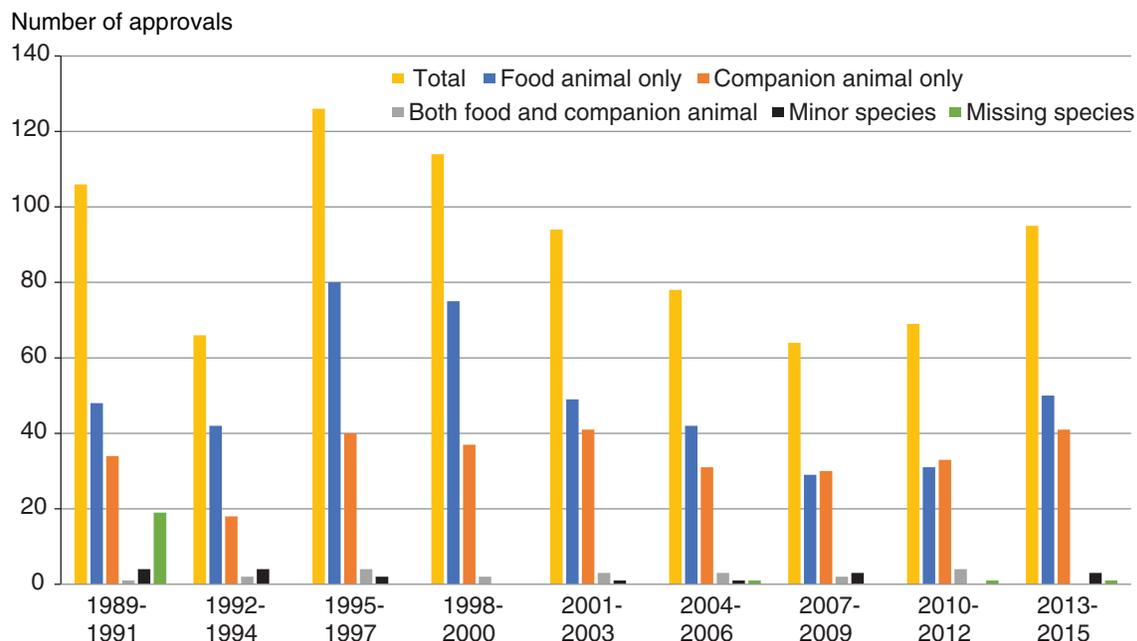
As noted previously, the number of nongeneric veterinary drug approvals has generally trended down since the late 1980s. There were also declines in the *total* number of veterinary drug approvals (generic plus nongeneric) (fig. 15). Between 1995 and 2009, the total number of approvals trended downward, and there has been an increase since about 2010.

In all time periods, the largest numbers of drugs approved were generally those for food animals, and the overall decline in the number of approvals appears to be largely due to a reduction in approvals of food-animal drugs. As the *number* of companion animal products remained fairly steady, the *share* of drugs approved for companion animals increased (fig. 15). Beginning in the early 2000s, the numbers of companion animal drug approvals have been very similar to those for food-animal production. Fig. 15 also shows that most products have not been approved for *both* companion and food animals.

As in the drug sector, a substantial portion of veterinary biologic activity is geared toward companion animals. Twenty-nine percent of active licenses⁴⁰ in 2016 were for companion animals (including felines, canines, equines, and pet birds) (fig. 16). Food animals (poultry, cattle, and pork) constituted 54.7 percent of products in active status in 2016. Of the food-animal categories, poultry constituted the large share (23.1 percent), followed by cattle (20.2 percent), and pork (11.4 percent).

⁴⁰Firms must maintain licenses for their veterinary biologic products in order to keep them in “active” status.

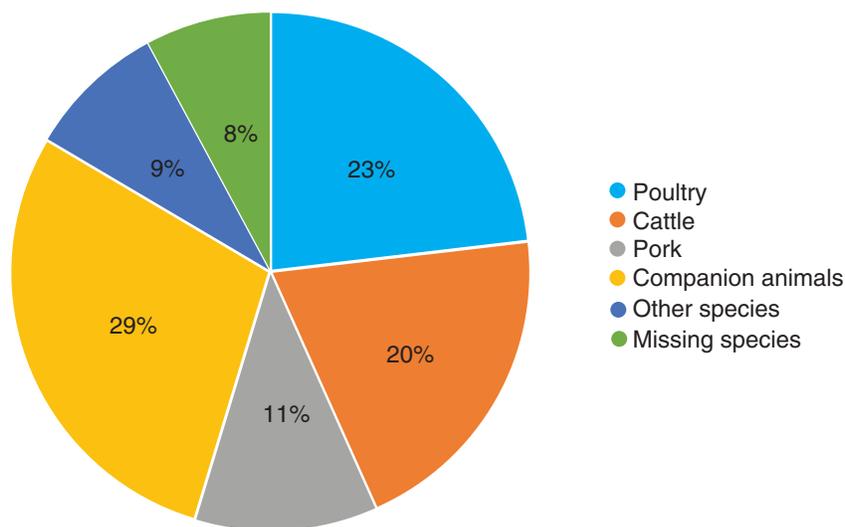
Figure 15
Number of veterinary drug approvals, 1989-2015, by treated species



Notes: Approvals include generics and exclude approvals for medical gases. Minor species include deer, ferrets, fish, goats, weasels, pigeons, primates, quail, rabbits, reindeer, rodents, sheep, bison, partridges, crustaceans, bear, wildlife, and wild or zoo cats.

Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

Figure 16
Shares of veterinary biologic licenses* active in 2016 by treated species



Notes: *A "license" is defined in this data as a unique combination of an establishment code and a product code; see USDA, Animal and Plant Health Inspection Service, Center for Veterinary Biologics (APHIS-CVB) Policy, Evaluation and Licensing Reviewer Manual for explanation of how product codes are defined. Establishment codes refer to unique product manufacturers. New product codes may be given if a firm purchased product licenses from another firm. An individual establishment code x product code combination may have multiple species associated with it. "Other species" include alligators, apes, goats, sheep, coyote, doves, elephants, elk, deer, ferrets, fish, foxes, deer, mink, mice, rabbits, raccoons, rats, and reindeer.

Source: USDA, Economic Research Service tabulations from APHIS-CVB data. See Appendix for more description.

Antibiotics and Vaccines Form the Largest Shares of Animal Drugs and Biologics Approved

Veterinary pharma companies can make choices to invest in drugs according to the type of drug as well as the treated species. Table 6 shows the number of new product approvals according to three categories of drug (antibiotics, parasiticides, and other drugs), as well as by animal category (“companion” and “food” animal).⁴¹ Antibiotics constitute the largest group of drug approvals in almost all periods. Notably, the share of drugs in the “other” category rose over time, which may be due to companion animal drugs’ differences from food-animal drugs. For example, end-of-life drugs for companion animals (such as drugs for cancer, osteoarthritis, and diabetes) have become more frequent (Yarbrough, 2016), but these are not products used in food animals.

In table 6, we also examine whether different types of drugs are developed for companion animals than for food animals. Such differences, if they exist, may affect food-animal-product development as animal pharma companies increase their investments in companion-animal products at the expense of food-animal products. Table 6 shows that the most common type of drug developed for food animals was antibiotics, while the most common type of product developed for companion animals belonged to the “other” category. In 1989-2015, 77 percent of new food-animal drug approvals were for antibiotics, while 54 percent of companion-animal drugs were in the “other” category.

Figure 17 shows the share of active veterinary biologic licenses by type of product for both food and companion animals. Vaccine licenses dominated at 54 percent, but a sizable share (24 percent) of products were in the “other” category, which includes bacterin, antibody, and antitoxin products.

Generics Constitute a Significant Share of New Animal-Drug Approvals

Animal pharma companies may decide to invest in marketing generic drugs, rather than generating new drugs. Figure 18 shows the number of drugs approved from 1972 to 2015—a timeline that shows trends both before and after the introduction of generic drugs in 1992. Two observations are clear. First, the downward trend in product approvals began before 1989. Second, generics have constituted a significant share of products approved since they became available; between 1992 and 2015, 52 percent of all product approvals were generics. The number of new animal drug approvals with a new ingredient—one indication of innovation in the pharmaceutical market—has also declined over time. Further analysis is necessary to discern whether the number of “original” new animal drug approvals was affected by the introduction of generics.

Generic approvals have not varied widely by drug type or treated species (table 7). From 1992 to 2015, generic approvals were most likely to be antibiotics (57 percent) while “other” drugs were least likely (46 percent). Percentages by type of drug show no strong trends over time.

From 1992 to 2015, generics were also more likely to be food-animal drugs (56 percent) than they were to be companion-animal drugs (50 percent). Again, there was no strong trend over time in the likelihood of either food or companion animal drugs to be generics.

⁴¹Antibiotics are characterized according to ingredients in the drug, and do not include all antimicrobials. For example, arsenicals are antimicrobials but are not characterized as antibiotics. See Appendix for methodology in classifying drugs. The “other drug” category includes a wide array of drugs, such as hormones, painkillers, expectorants, and cancer drugs.

Table 6

Veterinary drug approvals by type of product and treated animal type, 1989-2015

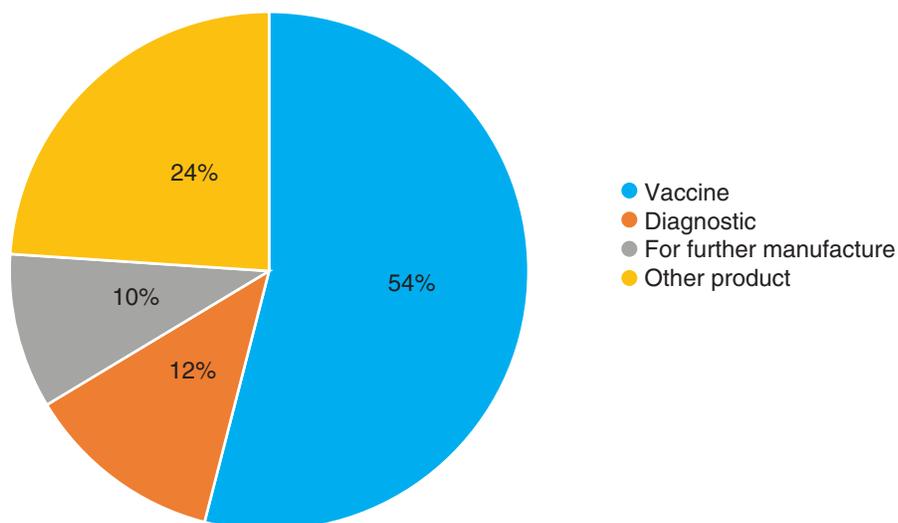
	Time period									
	1989-2015	1989-1991	1992-1994	1995-1997	1998-2000	2001-2003	2004-2006	2007-2009	2010-2012	2013-2015
All products										
Approvals	812	106	66	126	114	94	78	64	69	95
Antibiotics	449	56	43	82	71	43	39	28	35	52
Parasiticides	112	13	6	12	15	26	12	8	13	7
Other	251	37	17	32	28	25	27	28	21	36
Share (%) of total product approvals										
Antibiotics	55	53	65	65	62	46	50	44	51	55
Parasiticides	14	12	9	10	13	28	15	13	19	7
Other	31	35	26	25	25	27	35	44	30	38
Food-animal products										
Approvals	467	49	44	84	77	52	45	31	35	50
Antibiotics	358	32	39	71	63	38	32	22	23	38
Parasiticides	39	6	2	3	4	5	5	3	8	3
Other	70	11	3	10	10	9	8	6	4	9
Share (%) of food-animal product approvals										
Antibiotics	77	65	89	85	82	73	71	71	66	76
Parasiticides	8	12	5	4	5	10	11	10	23	6
Other	15	22	7	12	13	17	18	19	11	18
Companion animal products										
Approvals	326	35	20	44	39	44	34	32	37	41
Antibiotics	80	9	6	11	9	6	6	6	14	13
Parasiticides	71	7	3	9	11	20	6	5	6	4
Other	175	19	11	24	19	18	22	21	17	24
Share (%) of companion animal product approvals										
Antibiotics	25	26	30	25	23	14	18	19	38	32
Parasiticides	22	20	15	20	28	45	18	16	16	10
Other	54	54	55	55	49	41	65	66	46	59

Notes: Drugs with ingredients that may be used as parasiticides or antibiotics are characterized as antibiotics. Food-animal products may also be approved for companion animals or minor species. The same is true for the companion animal products. Does not include medical gases.

Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals. See Appendix for more data description.

Figure 17

Shares of veterinary biologic licenses* active in 2016, by type of product

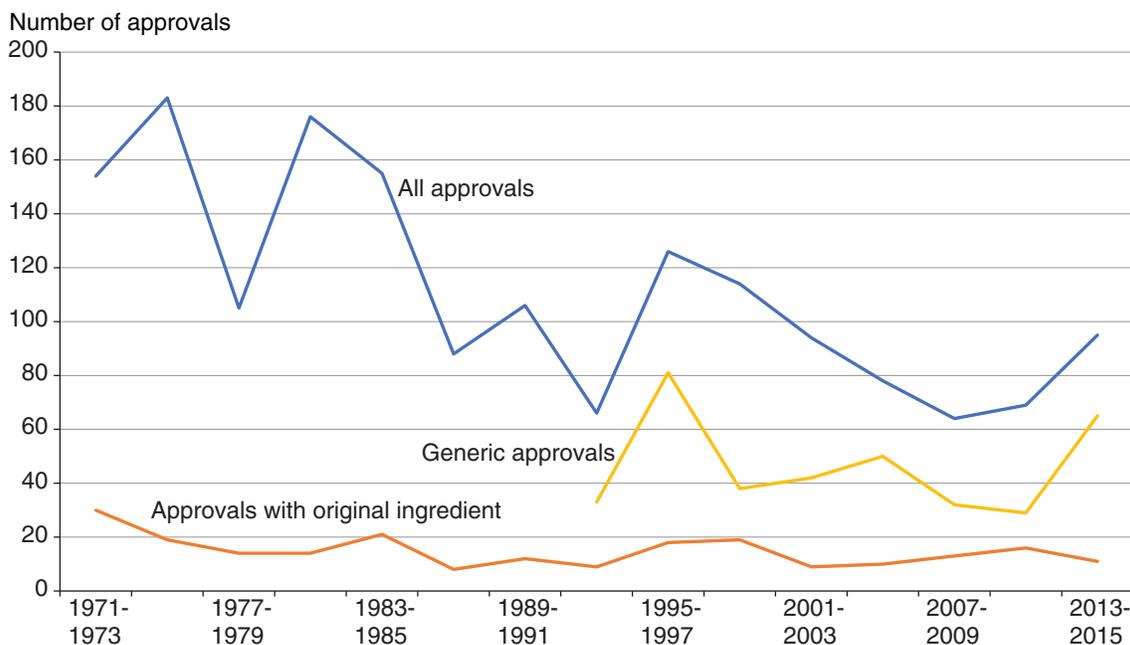


Notes: *A "license" is defined in this data as a unique combination of an establishment code and a product code; see the CVB Policy, Evaluation and Licensing Reviewer Manual (available online) for explanation of how product codes are defined. Establishment codes refer to unique product manufacturers. New product codes may be given if a firm purchased product licenses from another firm. "Other products" include antibody products, antitoxins, bacterin-toxoids, bacterins and bacterial extracts, toxoids, and miscellaneous. See Appendix for listing of products in "For further manufacture" category.

Source: USDA, Economic Research Service tabulations from USDA, Animal and Plant Health Inspection Service, Center for Veterinary Biologics (APHIS-CVB) data.

Figure 18

Number of veterinary drug approvals, veterinary drug approvals with original ingredient, and generic veterinary drug approvals, 1972-2015



Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

Table 7

Shares (percent) of new animal drug approvals that were generic, by animal type and type of drug, 1992-2015

	Time period								
	1992-2015	1992-1994	1995-1997	1998-2000	2001-2003	2004-2006	2007-2009	2010-2012	2013-2015
Food-animal approvals	56	52	70	34	37	70	68	45	76
Companion animal approvals	50	45	56	41	55	62	38 ^a	37	63
All approvals	52	48	64	36	45	64	50	40	68
Antibiotic approvals	57	61	72	33	33	66	64	42	80
Parasiticide approvals	49	0 ^b	18 ^b	40	69 ^b	75	50	46	43 ^b
Other approvals	46 ^b	35 ^b	59 ^{b,c}	39	40 ^{b,c}	56 ^b	36 ^b	33 ^b	57 ^b

Notes: Approvals for food and companion animals include only those approvals with species listed. Hence, the share of food-animal approvals that are generic is the number of generic products approved for food animals divided by the number of products approved for food animals. Drugs listed here may be approved for both food and companion animals and do not include medical gases. Drugs with ingredients that may be used as parasiticides or antibiotics are characterized as antibiotics. ^aStatistically significantly different at the 5 percent level from proportion for food animals. ^bStatistically significantly different at the 5-percent level from proportion for antibiotics. ^cStatistically significantly different at the 5-percent level from proportion for parasiticides.

Source: USDA, Economic Research Service analysis of data from Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

Trends in the Development of New Veterinary Antibiotics

As detailed in prior sections, demand for antibiotics used in food-animal production may be changing due to shifting demands for meat and animal products, consumer preferences, and regulations. These shifts in demand may alter the type of products developed by animal pharma. Competition for R&D dollars for companion-animal drug development and the presence of generic competitors may also shift decisions to develop new antibiotics.

Several firms have made public statements regarding the commitment to fighting antibiotic resistance. For example, in 2016 Elanco announced an antibiotic stewardship plan that included a commitment to develop “animal only” antibiotics as well as non-antibiotic alternatives (Happe, 2016). Other industry statements suggest that any new antibiotics approved for food-animal use are not likely to be those deemed “critically important”⁴² to human medicine (Shryock and Richwine, 2010).

Are Approvals for Veterinary Antibiotics Declining Like Those for Human Antibiotics?

Many antibiotics developed for use in animal production are “cast-offs” from products originally intended to be marketed to humans, reflecting the fact that basic research for animal and human products is interconnected scientifically and through business structures. The decline in the development of new human antibiotics, much discussed in the policy literature and public press (e.g., Theuretzbacher, 2015), suggests there may a similar decline in the development of new antibiotics for food-animal production. As shown in table 6, the number of animal antibiotics approvals has generally been declining. For human medicine, a partial recovery in the number of new antibiotics was driven by the 2012 Generating Antibiotics Incentives Now (GAIN) Act, which allows expedited review of qualified antibiotics (Theuretzbacher, 2015). This human pharma development appears also to have elicited a slight increase in the number of animal antibiotics approved in 2013-15. It is too soon to know if the increase in approvals represents a temporary effect as drugs in the existing pipeline move through regulatory review more quickly, or if these policies have permanently increased the rate of drug development.

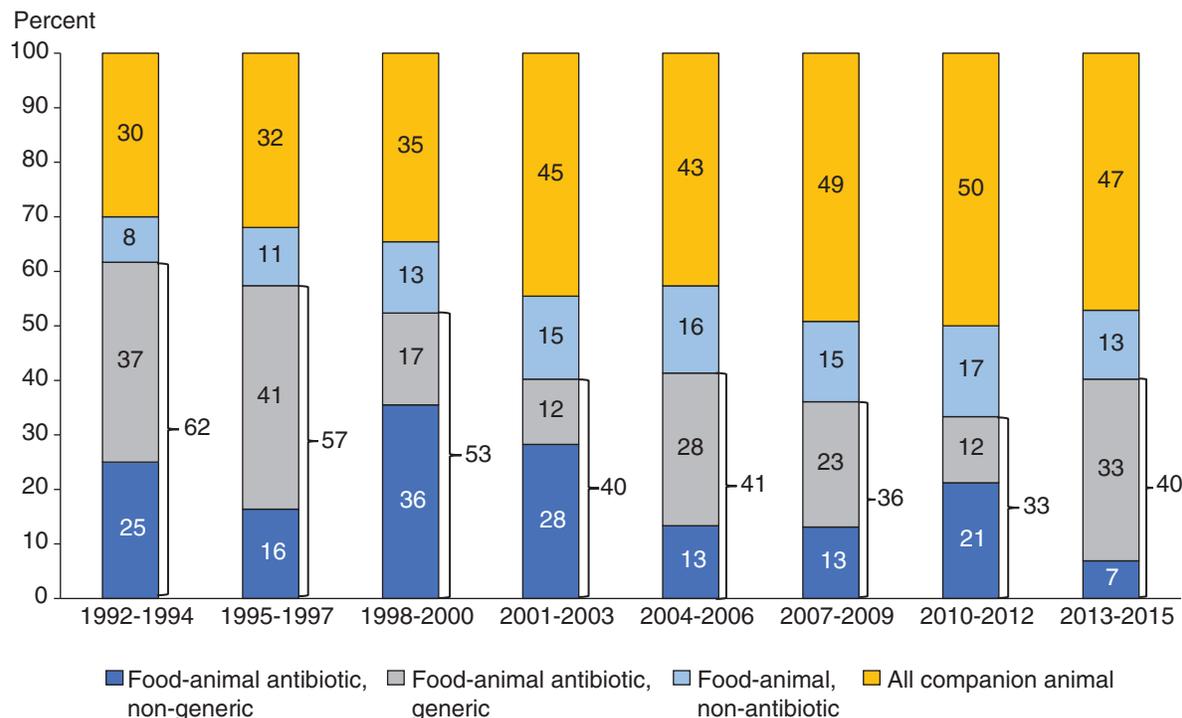
The *number* of veterinary antibiotics approved has declined (see table 6), but this partly reflects an overall decline in the number of animal drug approvals. However, aside from the uptick in 2013-15, food-animal antibiotics as a *share* of all veterinary drug approvals has also declined (fig. 19).

Figure 19 also suggests that R&D for *new* food-animal antibiotics is declining. Introductions of new nongeneric food-animal antibiotics appear to be declining, while generics make up an increasing share of new approvals.

⁴²The World Health Organization (WHO) has compiled a list of antibiotics and ranked them according to their importance to human medicine. The “critically important” antibiotics are those for which the antibiotic class is the sole therapy to treat serious bacterial infections in people (WHO, 2017).

Figure 19

Share of new veterinary drug approvals by type of treated species, by type of treated species for food animals (antibiotic or non-antibiotic), and status for food-animal antibiotics (generic versus nongeneric), 1989-2015



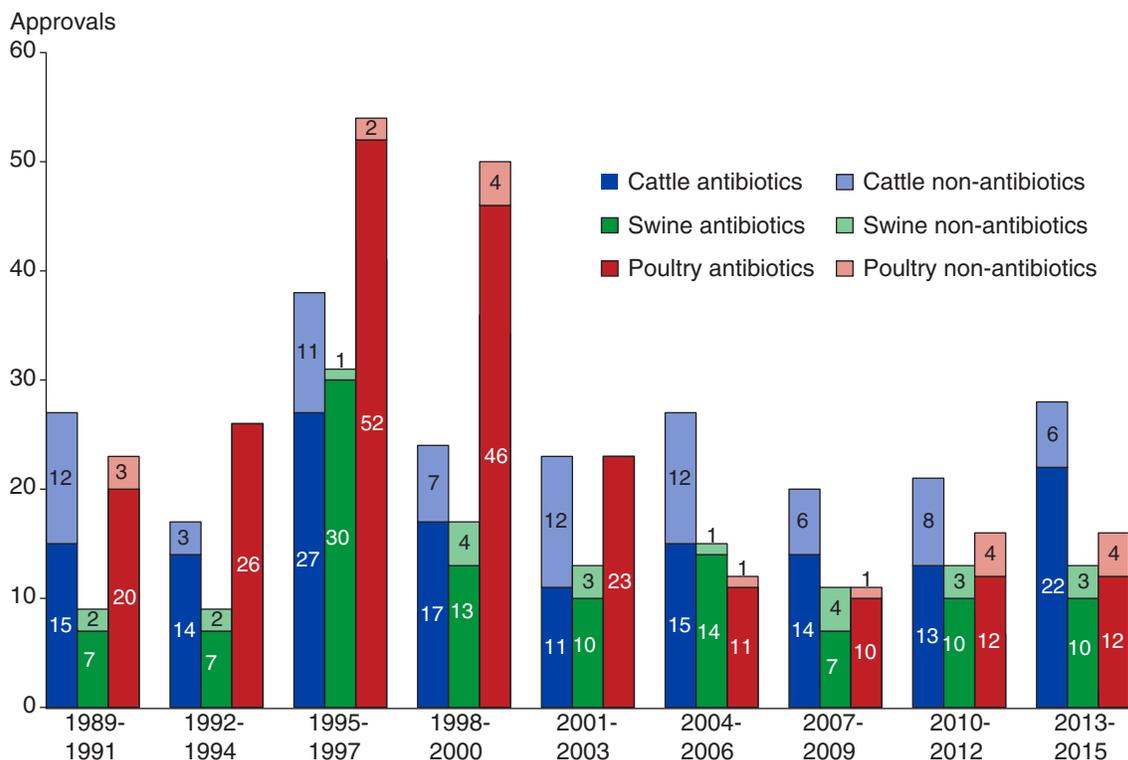
Note: Analysis does not include approvals of products for minor species or products without a species listed; combined, these excluded products comprise 2.5 percent of approved products between 1992 and 2015. The “food animal” category includes the few products approved for both companion or food animals. Medical gases are not included. Bars may add to greater than 100 due to rounding.

Sources: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine, Green Book reports of veterinary product approvals.

Is the Rise of “Raised without Antibiotics” Poultry Correlated With a Decline in the Number of Poultry Antibiotics Approved?

The trend in “raised without antibiotics” production has largely been in poultry, with the share of “raised without antibiotics” poultry reaching 44 percent of all poultry production in 2017. Therefore, we might expect to see a shift in poultry drug approvals away from antibiotics and toward non-antibiotics, and we might expect this shift to be larger in poultry than in cattle or swine approvals. “Raised without antibiotics” production of beef and pork remains a very small percentage of production, and organic milk (which also does not use antibiotics) comprised less than 5 percent of the milk market in 2013 (USDA ERS, 2014). Although the number of poultry drug approvals has declined overall since 1995, the poultry drugs that are still approved have been largely for antibiotics (figs. 20 and 21). Antibiotics’ share of poultry drug approvals was greater than the share of cattle and swine approvals for all periods before 2010. However, between 2010 and 2015, antibiotics’ shares of poultry drug approvals were lower than they had been earlier; between 1989 and 2010, 94 percent of poultry drug approvals were for antibiotics, while that share was 75 percent for 2010 to 2015. This trend suggests that poultry drug makers may, in fact, be shifting out of antibiotics, responding to the rise in “raised without antibiotics” production. Because of the long lag between research initiation and product approval, the effects of upward-trending “raised without antibiotics” production might not yet fully be captured in product approvals.

Figure 20
Number of food-animal new drug approvals, by treated species and antibiotics versus non-antibiotics, 1989-2015



Note: "Antibiotics" include parasiticides with antibiotic ingredients. Individual drugs may be approved for multiple species.

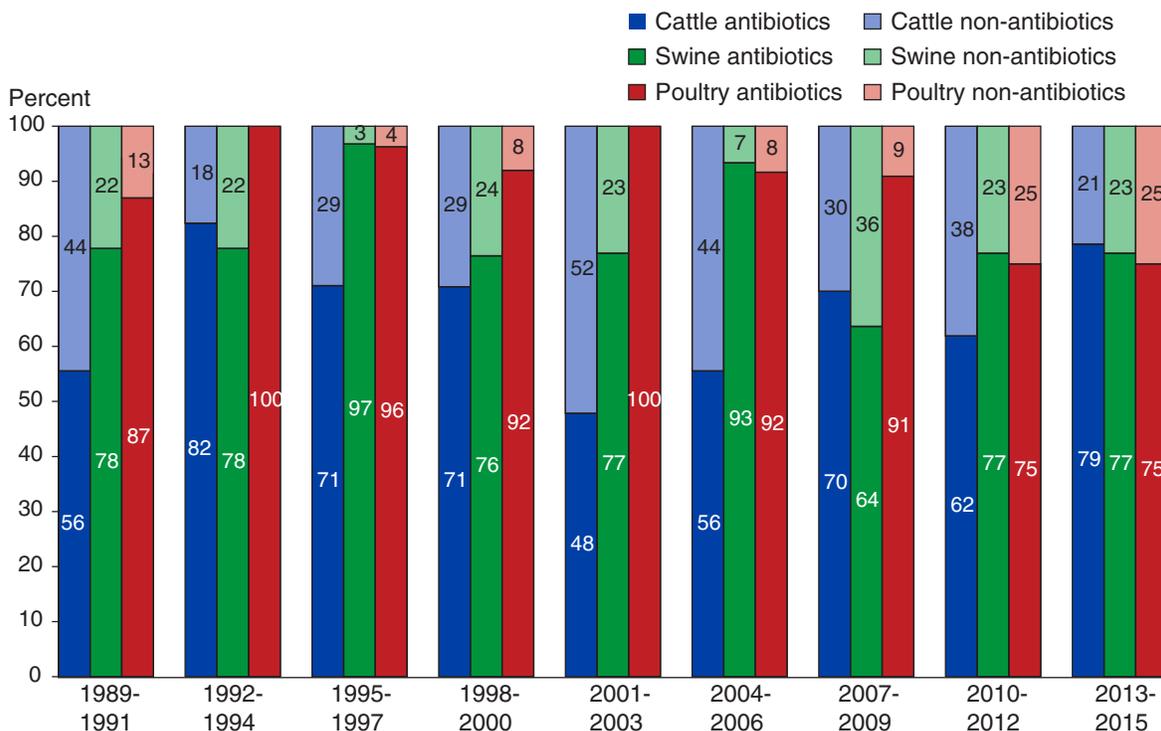
Sources: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

Are Fewer Medically Important Antibiotics Being Approved for Food-Animal Use?

U.S. regulations on antibiotics use in production have focused on antibiotics also used in human medicine. Antibiotics classes—mostly notably ionophores—deemed “currently not medically important” are not used to treat human illnesses. In 2017, FDA’s policies ended the use of medically important antibiotics for growth-promotion purposes—policy we might expect to result in development of fewer medically important antibiotics for animal use. Although the relevant policies were originally announced in 2013, any potential impact on drug development may not yet be identifiable because products that were already in the R&D pipeline may have been carried to market regardless of the regulation’s effects on eventual sales. The average development lag from identification of a new product idea to launch of a new product is 7 to 10 years (Animal Health Institute, undated).

Figure 21

Shares of food-animal veterinary drug approvals, by treated species and antibiotics versus non-antibiotics, 1989-2015



Note: “Antibiotics” include parasiticides with antibiotic ingredients. Individual drugs may be approved for multiple species. Shares are those of the drugs approved for the named species in the time period.

Sources: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

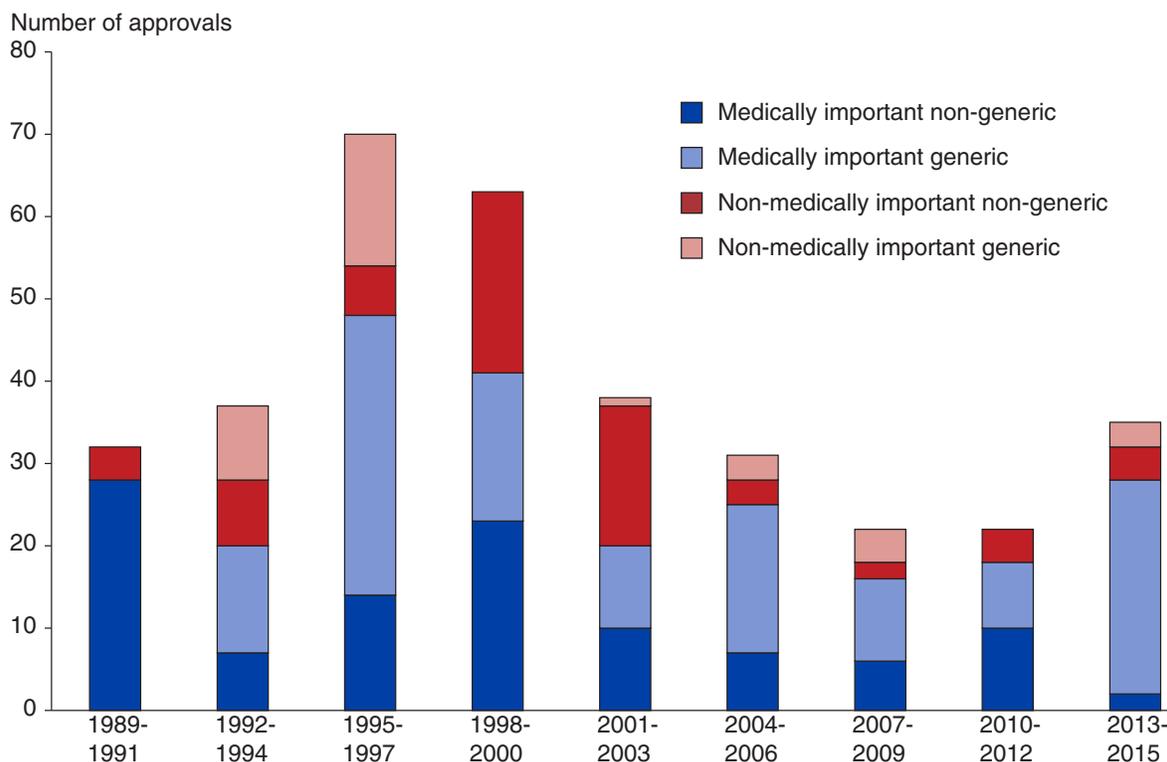
Figure 22 shows the number of livestock antibiotic approvals according to medical importance; most antibiotics in all time periods were medically important (70 percent since 1989). Figure 22 also supports figure 19’s finding that animal pharma companies are increasingly developing *generic* food-animal antibiotics rather than *nongeneric* food-animal antibiotics. This suggests the antibiotic development is not focused on developing innovative products. However, while new approvals for nonmedically important nongeneric antibiotics for food animals have declined, they are not zero. Thus, some innovation in this space still is occurring.

Effects of Approval Regulation on New Antibiotic Product Development

In response to concerns over the use of antibiotics in animal agriculture, FDA passed Guidance for Industry #152 (GFI #152) in 2003 (U.S. FDA, 2012 and 2013). GFI #152 requires new animal drug applications to study the likely effect of the drug on antibiotic resistance. If a drug shows significant risks of increasing resistance to antibiotics used in human medicine, it may have its label uses restricted. For example, the drug may not be approved to treat as many conditions, or it may be available only by prescription. If the risks are deemed too high, the drug may not be approved at all. Notably, this regulation covers development of new antibiotics and should not be confused with the regulations on antibiotics use previously discussed.

Figure 22

Number of food-animal antibiotic approvals, by medical importance and generic status, 1989-2015



Sources: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine Green Book reports of veterinary product approvals.

From a policy perspective, the broad research question is whether the regulation affected innovation. A large body of work examines whether regulation may encourage or hinder regulation (e.g., Jaffe and Palmer, 1997; Ambec et al., 2013; Grabowski et al., 1978). More narrowly, policymakers may be interested in whether regulations on antibiotic development in animal pharma hinder approval of new antibiotics for food animals. If so, then relaxing regulations might be one policy lever to increase new drug approvals.

GFI #152 may affect the supply of antibiotics for animal agriculture in two ways. First, it may directly reduce the number of drug applications that are approved, if FDA rejects applications deemed too risky. Second, it may indirectly reduce the number of antibiotics submitted to FDA because GFI #152 raises the cost of getting approval and reduces the likely value of antibiotics. (If they are approved, they may still have new label restrictions imposed on them.) Facing choices about how to allocate R&D funds, drug companies might choose to focus on non-antibiotic drug candidates or antibiotics not subject to greater scrutiny under GFI #152.

To investigate this question, we conducted a regression analysis on all nongeneric FDA-approved drugs. We assigned every nongeneric FDA-approved drug into sets of narrowly defined categories. These categories were based on (1) the species a drug was approved for, (2) the dispensing status, and (3) whether or not the drug was an antibiotic. We considered the seven species denoted “major species” by FDA (cattle, cats, chickens, dogs, horses, swine, and turkeys). The dispensing status can be “prescription” or “over-the-counter,” such that categories of drugs include “prescription antibiotic

drugs for chickens,” “over-the-counter antibiotic drugs for chickens,” and “prescription non-antibiotic drugs for dogs.” Given 7 species, 2 dispensing statuses, and 2 categories of antibiotic (antibiotic or not), we have 28 distinct categories of drug.

We then used a poisson regression analysis to see if there was an impact of GFI #152 (see box “Poisson Regression”). Specifically, we looked to see if there was a disproportionate decrease in the number of antibiotic drug approvals for food animals (cattle, chickens, swine, turkeys) after GFI #152 was passed. These are the drug categories specifically affected by GFI #152.

This methodology controls for the fact that the number of all animal drug approvals has been declining over time and that different drug categories have been declining at different rates. In essence, the methodology estimates what the average number of approvals were before and after the regulation within each category and then examines whether the change in the category of interest is different from the change in the other categories. In this way, it can be used to estimate what the number of new antibiotic approvals for food-animal use would have been with and without the regulation.

We found little to no evidence that GFI #152 had a negative effect on the number of approved drugs. As shown above, drug approvals were on a longrun declining trend in the years before and after 2003. However, we found the categories expected to be most affected by GFI #152 (antibiotics for food animals) actually decreased *less* than other categories after 2003. Does this mean GFI #152 actually boosted drug approvals, relative to a scenario where GFI #152 had never been implemented? It is unlikely. The relative increase in affected drug categories was driven by a rise in the number of prescription antibiotics for animals. This trend was underway before the passage of GFI #152 and disappeared completely when we included additional explanatory variables. To summarize, the drug categories most affected by GFI #152 did not experience a notable decrease in approvals (relative to other drugs), after it was implemented.

Poisson Regression

Regressions provide a way (1) to assess the correlation between data of interest (in our case, the number of drug approvals per year in different categories) and multiple explanatory variables and (2) to assess the probability these correlations would occur by chance under various assumptions. The most common regression method is called ordinary least squares. However, when the data being modeled has the nature of small integers (0, 1, 2, 3,...), as our counts of drug approvals do, then using ordinary least square regression violates some of the assumptions underpinning use and interpretation of the results. A poisson regression is an alternative regression approach suitable for modeling integer data such as our own (Wooldridge, 2010).

Summary and Conclusions

Antibiotics are an important revenue stream for the animal pharmaceutical industry. Regulatory changes, consumer preferences, and food-animal production practices to prevent disease exert downward pressure on the sales for antibiotics. On the other hand, increasing demand for meat from the United States and EU, whether for domestic consumption or for export, increases demand for antibiotics sales. These countervailing pressures affect what drug and biologic products the animal pharmaceutical industry chooses to research and develop. Further, the types and overall availability of new veterinary products affect food-animal production, consumer spending, and public health.

Overall, the U.S. and EU markets for antibiotics for food-animal production do not appear to be growing. U.S. antibiotics sales dropped by 30 percent between 2015 and 2017. Evidence from European countries suggests that overall antibiotics sales in those countries declined as a result of greater regulations. Additionally, the increase in consumer and retailer demand for food products raised with no or fewer antibiotics also exerts downward pressure on antibiotics sales.

Nevertheless, despite the range of downward pressures, antibiotics sales in the United States and EU could still increase as a result of rising meat, poultry, and milk production. Production growth will likely be due to increasing exports, largely to Asia. Trade agreements and restrictions will play into the magnitude of these changes in production. Low-probability but high-risk factors may also influence antibiotics sales for food-animal production. Livestock diseases once limited to other regions may become more prevalent in the United States and EU because of increasing globalization. Antibiotic resistance may reduce the efficacy of antibiotics in treating livestock diseases, potentially requiring higher doses (and more money spent) for effective treatment.

Concurrent with recent declines in antibiotics sales and demand, R&D dollars spent per new veterinary drug approval have trended upward, and new possibilities have arisen as investment opportunities for the animal pharmaceutical industry's R&D. Companion-animal drug approvals have been an increasing share of product approvals, suggesting that a larger share of R&D dollars have been devoted to companion animals rather than livestock. Since entering the market in 1992, generic drugs have formed a significant share of new drug approvals. If generic drugs compete with existing products, animal pharma may have responded by re-routing money from R&D toward marketing an existing product base. Likewise, declining sales of antibiotics in recent years suggest that R&D devoted to researching new animal antibiotics may also decline. The number of antibiotics developed for food-animal use has indeed declined, and antibiotics are declining as a share of new, approved animal drugs.

The trends and analysis described in this report set the stage for understanding whether the animal pharma industry needs to be incentivized to provide products to fulfill policy aims. One method of reducing use of medically important antibiotics in agriculture is the availability of cost-efficient alternatives. However, if the animal pharma industry is not developing such products, the government or other entities might decide to incentivize them. This has been the case for human antibiotics, where several policies have been enacted to encourage development. Efficient incentivization schemes are those that fund products that would not otherwise have been developed or have been developed at the desired rate. This report provides an initial, broad baseline for product development trends.

While this report provides an overview of topics related to antibiotics sales and development for food-animal use, it also generates a number of research questions. For example, how will the growing food-animal production in China, India, Brazil, and a number of smaller countries influence the animal pharma industry's sales of antibiotics and future R&D efforts? Will the declines in antibiotics sales in the United States and the EU continue? Has concentration in the animal pharma industry impacted innovation? Has the introduction of the ability to market generic veterinary drugs eroded innovation? How much does the animal pharma industry contribute to overall changes in agricultural productivity, and what might changes to animal pharma do to agricultural productivity? How has the introduction of new veterinary products historically changed meat or milk production and prices? Answering many of them will require an interdisciplinary effort of economists, veterinarians, epidemiologists, and livestock producers. It is an area with a rich array of possible research avenues, all pertinent to comprehending and combating the spread of antibiotic resistance.

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Appendix

Veterinary Drug Approvals

Compiling the Approval Data

Since 1989, the U.S. Food and Drug Administration (FDA) has published an annual report, called the Green Book, on all approved animal health products. The initial publication in 1989 ostensibly included all approvals completed before 1989 that had not been withdrawn at the time of publication. We obtained archived PDFs of the Green Book for each year through 2015 and used a text-mining program (written in Python) to extract every mention of a New Animal Drug Application code number. Because the Green Book is published each January, we assume drugs are approved in the year preceding the first year they appear in a Green Book. For example, we assume a drug first mentioned in the 2001 Green Book (published in January 2001) was approved in 2000. For drugs approved prior to 1989, the 1989 Green Book provides the approval date. We also use published listings of monthly drug approvals from the FDA-CVM website for 2016 and 2017. For this report, 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.

We cross-checked the New Animal Drug Application codes mentioned in Green Book editions with the FDA’s “Animal Drugs @FDA” website, which provides label information on every approved animal drug. We webscraped this website to obtain the full label information for each drug code pulled from the Green Book editions. This provided us with detailed information on each drug:

- Type of application (New Animal Drug Application or Abbreviated New Animal Drug Application): Most drugs submit New Animal Drug Applications, but generic drug applications submit an Abbreviated New Animal Drug Application.
- Approved Species
- Active Ingredients
- Dispensing status: Drugs can have over-the-counter, prescription, or veterinary feed directive dispensing statuses
- Associated patents

In some cases, information is missing. This is particularly true for products that were approved in the early years of FDA drug approval. We, therefore, search for the New Animal Drug Application or Abbreviated New Animal Drug Application numbers for products with missing information. Generally, we can find Federal Registry listings of these New Animal Drug Applications and Abbreviated New Animal Drug Applications via internet searches.

Assigning Types of Drug to Approvals

The compiled data provided us information on ingredients within each product. One of our goals is to assign types of drugs (for example, “antibiotics”) to the listed ingredients. We have ingredients listed as character variables. In order to characterize these ingredients, we perform text matching of the listed ingredients against lists of ingredients from other sources.

Characterizing antibiotics

First, we perform exact character-value matching of the listed ingredients in the NADAs and ANADAs to four lists of antibiotics from external sources. These sources are as follows:

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

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

The OECD’s list is notably a list of veterinary *antimicrobials*; thus, it includes more than just *antibiotics*. (Antibiotics are technically a subset of antimicrobials, even though the two terms are often used interchangeably.) We, therefore, find matches first using the WHO and FDA lists. If an ingredient is matched to the OECD list but not the WHO and FDA lists, we manually check it. In some cases, these ingredients were non-antibiotic antimicrobials, but in others, they were antibiotics. The use of multiple lists is important because there are slight variants to many names of antibiotics. We also conduct phonetic matches (for example, to match “cephalexin” with “cefalexin”). We manually check the matches, and then manually check the nonmatched ingredients. An entire list of antibiotic ingredients are found in Appendix tables A1 and A2.

To characterize the antibiotic class, we use the FDA’s Guidance for Industry 152 appendix, which characterizes antibiotics according to class (and degree of medical importance). Because not all specific antibiotic names are included in that list, we supplement with manual coding. These ingredients might be in products that have been withdrawn since their original approval. Others might be ingredients in products that were approved but not marketed.

Characterizing parasiticides

We perform a similar match to that for antibiotics. The sources of parasiticide ingredients we use are:

1. A poster from dvm360 entitled “A Practitioner’s Quick Reference to Selected Parasiticides” (2013)
2. The *Merck Veterinary Manual’s* “Ectoparasiticides Used in Large Animals” (Stitch, undated; available via the web)
3. The *Merck Veterinary Manual’s* “Ectoparasiticides Used in Small Animals” (Dryden, undated; available via the web)
4. The website parasitipedia.net

Appendix table A3 lists the parasiticide ingredients in approved FDA-CVM products.

Appendix table A1

Medically important antibiotic ingredients in approved FDA-CVM products

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

Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine (FDA-CVM) Green Book reports of veterinary product approvals, World Health Organization (2017), US FDA (2003b), US FDA (2017b), and OIE (undated).

Appendix table A2

Not currently medically important antibiotic ingredients in approved FDA-CVM products

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

Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine (FDA-CVM) Green Book reports of veterinary product approvals, World Health Organization (2017), US FDA (2003b), US FDA (2017b), and OIE (undated).

Appendix table A3

Parasiticide ingredients in approved FDA-CVM products

(s) - methoprene	eprinomectin	levamisole hydrochloride	piperonyl butoxide
albendazole	epsiprantel	lufenuron	praziquantel
amitraz	febantel	milbemycin oxime	pyrantel pamoate
amprolium	fenbendazole	moxidectin	selamectin
clorsulon	imidacloprid	niclosamide	spinosad
dichlorophene	imidocarb dipropionate	nitenpyram	sulfaquinoxaline
dichlorvos	ivermectin	oxfendazole	
doramectin	ivermectine	oxibendazole	
emodepside	levamisole	piperazine	

Source: USDA, Economic Research Service analysis of Food and Drug Administration, Center for Veterinary Medicine (FDA-CVM) Green Book reports of veterinary product approvals, dvm360 (2013), Stitch (undated), Dryden (undated), and parasitipedia.net.

Veterinary Biologics

Description of Data

We received data in 2017 from the USDA APHIS’s Center for Veterinary Biologics on licenses. The data provide the initial date of license approval, the establishment name and code, the product name and code, the product type, the species, and whether the product was active at the date of data gathering. The earliest year of approval was 1968 and the latest was 2016.

We define a license as a combination of establishment code and product code. Often, there are multiple observations with individual combinations of establishment and product codes; license “codes” may be duplicated. For example, two observations/licenses might have the same combination of establishment and product code, but have different species.

Through personal communications with APHIS staff, we discovered that information on licenses that are no longer active may not be complete. Hence, we focus only on active licenses (at the time of data retrieval). Of the licenses with initial approval dates extending to 1968, 24 percent were listed as active.

Methods of Characterizing Product Type and Species

Product type

To characterize type of product, we use the variable “Product Type.” We divide observations into “Vaccines,” “Diagnostics,” “For further testing,” and “Other.” The grouping is done according to the Appendix table A4 (below). All active licenses have product types listed.

Appendix table A4

Veterinary biologics groupings by product type

Original product type value	Grouping	
Vaccines	Vaccines	
Vaccines with bacterins/bacterial extracts/toxoids		
Diagnostics products	Diagnostics products	
For further manufacture: antibody products	For further manufacture	
For further manufacture: antitoxins		
For further manufacture: bacterin-toxoids		
For further manufacture: bacterins and bacterial extracts		
For further manufacture: diagnostic products		
For further manufacture: miscellaneous		
For further manufacture: toxoids		
For further manufacture: vaccines		
For further manufacture: vaccines with bacterins/bacterial extracts/toxoids		
Antibody products		Other products
Antitoxins		
Bacterin-toxoids		
Bacterins and bacterial extracts		
Miscellaneous		
Toxoids		

Source: USDA, Economic Research Service analysis of data received from USDA, Animal and Plant Health Inspection Service Center for Veterinary Biologics.

Species

Approximately 9 percent of active licenses did not have a species listed. Of this 9 percent, we were able to designate the species for a third of them using the first word of the “True name.” For example, on observations without a species name listed but with a true name of “Bovine Respiratory Syncytial Virus, Modified Live Virus” was given a species of “Bovine.” Species were grouped according to Appendix table A5.

Veterinary biologics groupings of species

Original species name value	Grouping
Avian	Poultry
Chicken	
Duck	
Fowl	
Turkey	
Egg	
Bovine	Cattle
Ruminants	
Porcine	Pork
Swine	
Feline	Companion
Canine	
Equine	
Pet bird (e.g., parrot, canary)	
Alligator	Other
Apes, monkeys	
Caprine	
Coyote	
Elephant	
Elk	
Fallow deer	
Ferret	
Fish	
Mink	
Mule deer	
Ovine	
Pheasant	
Pigeon	
Rabbit	
Raccoon	
Avian (Non-chicken, Turkey, Or Quail)	
Reindeer	
White-tailed deer	

Source: USDA, Economic Research Service analysis of data received from USDA, Animal and Plant Health Inspection Service Center for Veterinary Biologics.

Human Drug Approvals

FDA's website "Drugs@FDA" allows a user to download all products ever approved by FDA's Center for Drug Evaluation and Research. We download all of these products, and from them, we are able to characterize year of approval, generic status, and whether the product is a "new chemical entity."

R&D Spending in Veterinary Pharmaceuticals

We use updated data from Fuglie et al. (2011) on veterinary pharma R&D spending. This series includes R&D spending on animal health by U.S. firms at home and abroad. As noted in Fuglie et al. (2011), R&D spending is “estimated from company financial reports and as reported in Animal Pharm Reports” (p. 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.

As we will describe, in relation to human pharma R&D spending, there are different elements that can be captured when a firm reports R&D spending. Additionally, total R&D for an industry can be calculated differently by including different elements of R&D and/or different firms. The Fuglie numbers are generated either from summing together the individually reported R&D for animal pharma firms or from industry reports from Animal Pharm. Thus, they are self-reported by firms and include what firms consider R&D.

What do animal pharma firms consider R&D spending? The industry group HealthforAnimals (previously, the International Federation of Animal Health or IFAH) published the results of a recent “benchmarking” survey for the industry. In it, HealthforAnimals defined R&D costs as:

“all relevant internal costs, such as personnel, apportioned establishment costs, and allocated research costs, and those for outside resources such as CROs (Contract Research Organizations), field trials etc; and expenditure on defensive R&D” (HealthforAnimals, 2015, p. 32).

Thus, we might expect that when firms report their R&D in their annual reports or to the group Animal Pharm, they are considering the same elements. Notably, this definition of R&D includes post-market R&D (“defensive R&D”).

R&D Spending in Human Pharmaceuticals

The industry group Pharmaceutical Research and Manufacturers of America (PhRMA) publishes a series of R&D spending by its member companies. We used the reports published in 2017 and 2018 and 2013 annual industry profile reports from PhRMA to construct reported R&D spending for 1980 to 2017. 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 (e.g., Golec and Vernon, 2008; U.S. CBO, 2006). A 2006 Congressional Budget Office (CBO) report describes the difference as emerging from “differences in which drug companies are included in the samples and which expenditures are counted” (p. 7).

Specifically, the CBO writes that the PhRMA numbers:

“include all R&D spending in the United States by the association’s members (foreign and domestic) as well as expenditures abroad by U.S. firms and U.S. divisions of foreign firms. Spending by foreign companies that occurs outside of the United States is excluded” (p. 7).

The NSF numbers:

“cover only domestic R&D spending by firms ‘engaged in for-profit activity in the United States.’ They exclude all research and development not conducted in the United States,

including that performed by foreign subsidiaries of U.S. firms or by other foreign organizations. The National Science Foundation’s estimates also exclude spending on phase IV clinical trials (which are conducted after a drug has reached the market) and on the development of manufacturing processes – both of which PhRMA counts as R&D. In addition, NSF’s figures do not include R&D by pharmaceutical firms that sell their own products, if sales activities account for the largest share of payroll” (p. 7).

The CBO estimates that if the postmarket R&D, manufacturing processes, and excluded firms were included, then the NSF estimates would be similar to the PhRMA estimates, at least in 2003.

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 (described above).

Notably, PhRMA also publishes R&D spending on veterinary pharma products. However, these estimates are much lower than those reported by Animal Pharm (the industry group that collects data from major firms). The difference is likely due at least in part to the difference in the firms covered. If the listing of PhRMA firms in the 2015 Industry Profile is an indication of other years, none of the major standalone animal pharma firms is a PhRMA member. These firms include Zoetis, Virbac, and Ceva. Thus, the R&D of these major animal pharma firms would not be captured in PhRMA’s R&D statistics.

Both the human and animal pharma R&D numbers are self-reported by firms. In the period that we examine (1989 to 2015), tax credits for R&D have been in effect in the United States. The tax credit encourages firms to report their R&D, and possibly inflate it. As the CBO report suggests,

“R&D costs that companies report may be somewhat inflated because the federal research and experimentation tax credit gives firms an incentive to be expansive in classifying expenses as R&D-related....[CBO] has no evidence, however, about whether that is or is not the case.”

Thus, the numbers reported are likely pretax expenditures. Notably, both human and animal R&D would have similar incentives to overreport (if such a thing is taking place), suggesting that the ratio of human to animal pharma R&D dollars would not be impacted by potential over-reporting.

9-Year Moving Averages

Let R_t and N_t be R&D spending and drug approvals in year t . The centered 9-year moving averages are calculated as:

$$\bar{R}_t = \frac{1}{9} \left(R_t + \sum_{i=1}^4 (R_{t-i} + R_{t+i}) \right)$$

and

$$\bar{N}_t = \frac{1}{9} \left(N_t + \sum_{i=1}^4 (N_{t-i} + N_{t+i}) \right).$$

Estimating R&D Spending per Approval in Pharmaceuticals

We calculate R&D spending per drug approval as a centered 9-year moving average of real R&D divided by 9-year moving average of approvals, lagged 5 years. This reflects the lag between the R&D investment in the pharmaceutical industry and when products are approved.

The lagging 5 years means we calculate

$$S_t = \frac{\bar{R}_{t-5}}{\bar{N}_t}.$$