

Playing Chicken with Antibiotics: Previously Undisclosed FDA Documents Show Antibiotic Feed Additives Don't Meet the Agency's Own Safety Standards



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SUMMARY

Between 2001 and 2010, the United States Food and Drug Administration (FDA) quietly reviewed the safety of 30 penicillin and tetracycline antibioticⁱ feed additivesⁱⁱ approved for “nontherapeutic use” in livestock and poultry.ⁱⁱⁱ Nontherapeutic use refers to using antibiotics for growth promotion or to prevent disease in typically crowded, often unsanitary conditions.¹ NRDC obtained the previously undisclosed review documents from the FDA as a result of a Freedom of Information Act (FOIA) request to the agency and subsequent litigation made necessary by FDA’s failure to provide any of the requested documents.

FDA’s scientific reviewers’ findings show that *none* of these products would likely be approvable as new additives for nontherapeutic livestock use if submitted today, under current FDA guidelines. Eighteen of the 30 reviewed feed additives were deemed to pose a “high risk” of exposing humans to antibiotic-resistant bacteria through the food supply, based on the information available. The remainder lacked adequate data for the reviewers to make any determination and their safety remains unproven. In addition, FDA concluded in their review that at least 26 of the reviewed feed additives do not satisfy even the safety standards set by FDA in 1973.

To our knowledge, FDA has taken no action since the reviews to revoke approvals for any of these antibiotic feed additives (although two were voluntarily withdrawn by the drug manufacturer). The FDA does not disclose sales of specific animal drug products, and we have no information about the quantities of these specific antibiotic additives that were sold for livestock use or administered to food animals. However, we found evidence suggesting that at least nine of these additives are being marketed today, and all but the two voluntarily withdrawn additives remain approved for use today.

The significance of these findings extends far beyond the 30 antibiotic feed additives reviewed. FDA data indicate that the types of antibiotics in the reviewed additives—tetracyclines and penicillins—together make up nearly half of all the antibiotics used in animal agriculture. Other feed additives with these same antibiotics, including generics, that are approved for similar uses would likely pose a similar risk of promoting antibiotic resistance. This risk was recognized by FDA in 1977 when it proposed to withdraw approvals for animal feed additives containing penicillin and most tetracyclines.²

Furthermore, the use of tetracyclines and penicillins in animal feed is part of a larger problem of antibiotic overuse. Approximately 70 percent of all sales of medically important

antibiotics in the United States are for livestock use.³ Scientists have demonstrated that nontherapeutic use of antibiotics to raise livestock promotes drug-resistant bacteria that can migrate from livestock facilities and threaten public health. These bacteria can spread resistant traits to other bacteria, and some of these shared traits also can confer resistance to antibiotics used primarily in human medicine.⁴

Unfortunately, the FDA’s failure to act on its own findings about the 30 reviewed antibiotic feed additives is part of a larger pattern of delay and inaction in tackling livestock drug use that goes back four decades. A recent voluntary policy adopted by FDA, “Guidance #213,” recognizes the problem, but lacks meaningful requirements and seems unlikely to curb uses of the antibiotics reviewed here or any of the other problematic uses (for a number of reasons discussed further below). It is time for decisive action to help protect the public from the threat of antibiotic resistance. The FDA should:

1. Complete the decades-delayed process for withdrawing approval of penicillin and tetracyclines in animal feed, strictly limiting their use to treating sick animals and, in rare circumstances, to controlling disease outbreaks.
2. Initiate the process for withdrawing approval for all other classes of medically important antibiotics approved for nontherapeutic livestock use that are not shown to be safe.

In the face of the FDA’s continued inaction, Congress, food industry leaders, and consumers should step in to demand change. Congress should insist on real regulation of livestock antibiotic use as outlined in the Preservation of Antibiotics for Medical Treatment Act (PAMTA) in the House of Representatives⁵ and the Preventing Antibiotic Resistance Act (PARA) in the Senate.⁶ In the meantime, large food companies and consumers can reduce livestock antibiotic use by choosing meat and poultry supplied by producers that promote antibiotic stewardship in the livestock and poultry industry.

i Here we use “antibiotic” to refer to all antibacterial agents, including both synthetic antibacterials and those produced from a natural source. For convenience, and based on common usage, we use “antibiotic” throughout.

ii For convenience, “antibiotic feed additives” refers throughout to drug products added to both feed and water.

iii Hereafter, for ease of use, “livestock and poultry” is referred to only as “livestock.” Similarly, “livestock facilities” refers to both livestock and poultry facilities.

A BRIEF OVERVIEW OF ANTIBIOTICS, RESISTANCE, AND LIVESTOCK USE

Antibiotics are the miracle drugs of the past century; they transformed medical care by turning infections that often proved fatal or required amputation into easy-to-treat illnesses.⁷ Yet overuse and misuse of these medicines in both humans and food animals is causing rising rates of antibiotic resistance. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have repeatedly highlighted the risk of an impending post-antibiotic era due to growing resistance and have called for action, including the curtailment of inappropriate uses in livestock.⁸

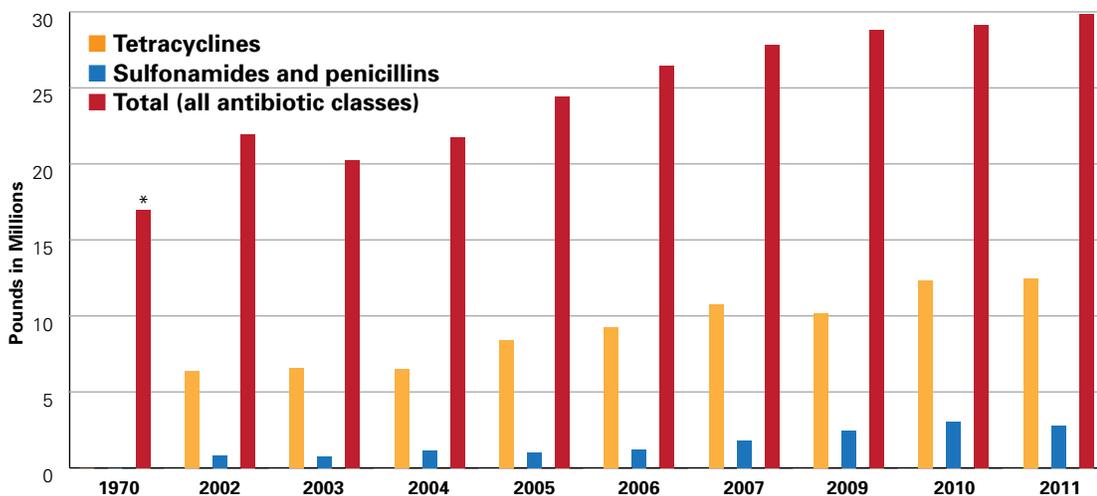
In a report on Antibiotic Resistance Threats in the United States, 2013, the CDC says that “[i]n most cases, antibiotic-resistant infections require prolonged and/or costlier treatments, extend hospital stays, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics.”⁹ The agency also warns that declining effectiveness of antibiotics will undermine “many life-saving and life-improving” procedures and treatments, such as “joint replacements, organ transplants, cancer therapy, and treatment of chronic diseases such as diabetes, asthma, [and] rheumatoid arthritis.”¹⁰

As U.S. production of meat and poultry products has grown, U.S. livestock farms have become larger, leading to more confinement and crowding and also to greater risk of

disease among the animals.¹¹ After the FDA approved the use of antibiotics in livestock feed in 1951, producers began relying on nontherapeutic use of antibiotics to speed animal growth and to prevent disease.¹² Studies by both livestock scientists and advocacy groups, while they have data gaps, suggest that the majority of all antibiotic use in U.S. livestock is for these nontherapeutic purposes, rather than for the treatment of sick animals.¹³

Using antibiotics at low doses for extended periods of time in crowded livestock facilities can lead to more drug-resistant bacteria that can outcompete other bacteria, and escape livestock facilities to threaten human health.¹⁴ A large chorus of scientists, health experts, and government agencies warns that the overuse and misuse of antibiotics in livestock production is contributing to the expanding public health crisis of antibiotic resistance, depleting the physician’s arsenal of antibiotics effective for treating infections in people. In its recent report, CDC notes that “much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe”¹⁵ and emphasizes that antibiotic overuse in both human medicine and livestock production is contributing to the problem of resistance.¹⁶ The report notes that antibiotic resistance is associated with at least 2 million illnesses and 23,000 deaths each year¹⁷ and shows that as newer antibiotics become less effective, older antibiotics may matter more.¹⁸

Figure 1: Estimated use of tetracyclines and penicillins/sulfonamides from 1970 to 2011 in livestock production.



Numbers for 1970 and 2002-2011 are based on estimates from the FDA and quantities sold domestically as reported by AHI and to the FDA. Penicillin and sulfonamides were reported together.

* No estimate of penicillin and tetracycline use is available for 1970. (Total=all antibiotic classes.)

Source: Data for graph compiled from several sources. Animal Health Institute, <http://www.ahi.org/archives/2008/11/2007-antibiotics-sales/>; The Poultry Site, <http://www.thepoultrysite.com/poultrynews/7985/antibiotic-use-in-us-animals-rises-in-2004/>; Food and Drug Administration “Summary Report on Antimicrobial Sold for Food Producing Animals-2009,” <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf>; Food and Drug Administration, “Summary Report on Antimicrobial Sold for Food Producing Animals-2010,” <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm277657.pdf>; Food and Drug Administration, “Summary Report on Antimicrobial Sold for Food Producing Animals-2011,” <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf>; Food and Drug Administration, “Statement of Gregory J. Ahart, Director, Human Resources Division before the House Committee on Interstate and Foreign Commerce on Food and Drug Administration’s Regulation of Antibiotics Used in Animal Feeds,” <http://www.gao.gov/assets/100/98536.pdf>

PENICILLINS AND TETRACYCLINES: USE IN ANIMAL FEED AND FOR HUMAN HEALTH

The reviewed antibiotic additives—penicillins and tetracyclines—are also important for treating human disease. In the U.S. in 2011, penicillins accounted for 44 percent of the total antibiotics sold for human medicine, and tetracyclines accounted for 3.5 percent.¹⁹ The World Health Organization lists penicillins as critically important for human medicine and lists tetracyclines as highly important.²⁰ The FDA itself recognizes both as highly important, even under its limited criteria whereby antibiotics are designated “critically important” only if the drugs are used to treat gut pathogens that cause foodborne illness.²¹ A partial listing of continuing medical uses of these drugs is provided in Table 1, below.²² Unfortunately, penicillins and tetracyclines are no longer effective in fighting some infections because of increased resistance, decreasing options for treatment.²³

Table 1: Overview of common medical conditions treated with penicillins and tetracyclines

Antibiotic Class	Antibiotic	Common Uses in Human Medicine ²⁴
Penicillins	Penicillin G	Syphilis Bacterial meningitis
	Ampicillin	Bacterial meningitis Leptospirosis Complicated UTI (kidney complication)
Tetracyclines	Tetracycline	Eye infection Early stages of syphilis Ehrlichiosis (spread by ticks and fleas)
	Doxycycline*	Chlamydia Gonorrhea Bronchitis Tularemia Lyme Disease

*Specific antibiotic not used in livestock, but cross resistance between antibiotic used in livestock and this antibiotic has been observed.²⁵

At the same time, tetracyclines and penicillins are among the most commonly used antibiotics in livestock production in the U.S. In 2011, 42 percent of antibiotics used in animals were tetracyclines and 6.5 percent were penicillins (Figure 1).²⁶

ANTIBIOTIC-RESISTANT BACTERIA CAN ESCAPE LIVESTOCK FACILITIES TO THREATEN PUBLIC HEALTH

A rich body of scientific literature, reinforced by the latest CDC report on emerging antibiotic resistance, shows that antibiotic-resistant bacteria bred in livestock facilities can make their way off the farm in a number of ways. People who work with livestock or in meat production/processing can carry the resistant bacteria into their communities.²⁷ Resistant bacteria can travel from the farm in air or water, can wind up in the soil when manure is applied to crops, which in turn can end up on fruits and vegetables, and can be found in meat on retail shelves.²⁸ Even insects and rats can carry antibiotic-resistant bacteria from farms to surrounding communities.²⁹ There is mounting evidence that antibiotic-resistant bacteria that originate in livestock are reaching our communities and homes.³⁰

Researchers have also demonstrated that the overuse and misuse of one antibiotic can actually lead to bacterial resistance to other antibiotics. This means that nontherapeutic use of penicillins and tetracyclines in animal feed can compromise the effectiveness of other medically important antibiotics that were not used in livestock facilities.³¹ This occurs through mechanisms described by scientists as “cross resistance” or “co-resistance.”³² (See box on antibiotic resistance).

Antibiotic resistance: How antibiotic use increases the population of resistant bacteria

Mutation and multiplication

Bacteria multiply rapidly. Each time this happens, there is a small chance that a gene in a bacterium will mutate in a way that makes it resistant to a particular antibiotic.

While new resistance genes can and do arise, bacterial resistance and associated genes have long existed, although usually in very low numbers.³³ Using an antibiotic, for instance, for growth promotion and disease prevention purposes, allows resistant bacteria that can withstand the antibiotic to survive and multiply. This creates many new bacteria that carry the same resistance gene, while bacterial populations susceptible to antibiotics die off, and ultimately increases the overall population of antibiotic-resistant bacteria.³⁴

Gene sharing and multiplication

Bacteria that are resistant to antibiotics can, in some cases, pass a resistance gene or 'trait' on to other bacteria, essentially "teaching" them how to endure an antibiotic. One or more resistance genes can be passed from one bacterium to another. This means that a bacterium can become resistant to an antibiotic it was never exposed to. This can even occur between different types of bacteria.³⁵ This gene-sharing can occur in any environment, including on the farm; in air, water, and soil; and in the community, including in the animal and human gut.³⁶

Cross resistance: A resistance trait that confers resistance to multiple antibiotics

Sometimes a bacterium's ability to resist one antibiotic enables it to resist other antibiotics as well, even those it was not exposed to. In simple terms, a bacterium can figure out, and/or share with a neighbor, a way to fend off antibiotics that are similar in structure or mechanism. Resistance to drugs both within a class of antibiotics or across multiple classes of antibiotics can be shared in this way. For example, as indicated in Table 1, bacteria that are resistant to oxytetracycline can also be resistant to Doxycycline, another tetracycline used only in human medicine.³⁷

Resistance traits that are shared can also confer resistance to drugs across antibiotic classes. A prime example of such a trait is the presence of antibiotic "pumps" in the bacteria. These literally pump out antibiotics from bacterial cells, and thereby make bacteria resistant.³⁸ Some of these pumps are very versatile and can pump out practically all classes of antibiotics currently used in medicine.³⁹ When this trait is transferred from one bacterium to another, the recipient bacterium can now withstand any antibiotic that the pump works on.

Co-resistance: Clusters of resistance traits that confer multidrug resistance

The ability of bacteria to move around and share genes also enables them to accumulate a cluster of resistant genes or traits in a single transferrable unit.⁴⁰ In one extreme case, ten resistance genes to eight different classes of antibiotics were found in such a unit.⁴¹ This can lead to an increase in multidrug resistance in the population when even one of these antibiotics is used, resulting in the selection of bacteria that have received the cluster from their neighbors. For years the USDA, FDA, and CDC have been testing for several known clusters of resistant genes, such as the resistance (and transferable) unit ACSSuT (resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline), and such clusters are often detected.⁴² The problem of co-resistant bacteria is well known in both livestock production and human medicine.

MAIN FINDINGS OF THE FDA REVIEW

NRDC obtained copies of the FDA review documents following litigation over a Freedom of Information Act (FOIA) request.⁴³ The documents tell a story of FDA's continuing inaction on antibiotic use in livestock even after the agency's own re-examination of 30 livestock antibiotic feed additives, some of which have been allowed for livestock use since the 1950s,⁴⁴ showed that these approved antibiotics have not been shown to be safe.⁴⁵ (For further details on the documents, see Appendix.) Starting in 2001 and concluding in 2010, FDA scientists, with expertise in fields such as veterinary medicine and microbiology, reviewed livestock antibiotic feed additives containing penicillin and/or tetracyclines.⁴⁶ The review was triggered by legislation in 2001 that set aside money for the FDA to work on antibiotics,⁴⁷ and was discontinued in 2010 for unknown reasons.⁴⁸

The FDA scientists reviewed the livestock feed additives, listed by NADA (New Animal Drug Application) number in Appendix I, according to two sets of criteria: safety regulations adopted by FDA in 1973 and FDA's 2003 guidelines for evaluating the safety of new animal antibiotic drugs (see sidebar).

The findings of the FDA review are troubling. Of the 30 reviewed antibiotic feed additives, 26 have never met the safety criteria established by FDA in 1973.⁴⁹ The 1973 safety requirements mandated that drug manufacturers submit scientific studies that addressed several criteria, including evidence that establishes that the nontherapeutic use of the antibiotics in animal feed did not promote resistance to antibiotics used in human medicine (see sidebar).⁵⁰ In addition to the 26, three other antibiotic additives were found not to have met the 1973 safety requirements (and thus were not proven to be safe), although the requirements may not have applied.⁵¹ Of the 30 reviewed feed additives, only one was found by FDA (in 1986) to meet the 1973 safety standards; however it was found to have failed the agency's standard for efficacy.⁵² It too remains approved for use.

Furthermore, when these previously approved antibiotic feed additives were evaluated against the FDA's 2003 antimicrobial safety guidelines (Guidance #152) for the evaluation of a new animal drug,⁵³ the agency found that 18 of the 30 antibiotic feed additives posed a high risk of exposing humans to antibiotic-resistant bacteria through the food chain. While FDA did not have sufficient data to conduct a comprehensive risk assessment for any of the 30 additives, it did have enough information to conduct an abbreviated

risk assessment for these 18 additives, which varied in the level of detail in the assessment. In all of these cases, FDA concluded that, based on the information available, these were "high risk" uses. For the remaining 12 additives, the drug manufacturers had not provided sufficient evidence for FDA to even determine the level of risk for human health posed by the additives, let alone to determine that the additives are safe as used (see Figure 1). Thus, none of the 30 reviewed feed additives could likely be approved in their current forms today.

Guidance #152 calls for the characterization of safety through the assessment of hazard (or level of risk) before approval of all new animal drugs. This allows the FDA to set the right restrictions for use of the drug in order to manage risk: under Guidance #152, high-risk drugs could only be approved for treatment of individual animals for short periods of time (less than 21 days).⁵⁴ Yet, the existing approvals for these 18 "high-risk" feed additives would allow much wider use. They are approved for over-the-counter use for long periods of time with no restriction on the number of animals to which they are administered. Thus, they could not be approved in their current forms today. The other 12 feed additives could not be approved today unless their safety was established⁵⁵ and FDA concluded that it did not even have sufficient information to estimate risk (see Appendix I).

The FDA has not withdrawn approvals for any of the reviewed antibiotic feed additives, even though the agency is required to do so when a drug is not proven to be safe.⁵⁶ FDA did send letters to "sponsors" (sponsoring company) in 2004 for six of these antibiotic feed additives deemed "high risk," requesting information to address concerns that the additives might promote antibiotic resistance (see Appendix III). The FDA records do not show that any of the sponsors provided additional studies that addressed the FDA's concerns (see Appendix III). Nor do the documents show that FDA took any further action.⁵⁷

The FDA does not disclose sales of specific animal drug products, and we have no information about the quantities of these specific antibiotic additives that were sold for livestock use or administered to food animals. However, we found evidence suggesting that at least nine of these feed additives are being marketed today (see Appendix II), and all but two apparently voluntarily withdrawn additives remain approved for use today.⁵⁸

FDA's Criteria for Evaluating the Safety of Approved Feed Additives

1973 Criteria (21 C.F.R. § 558.15)⁵⁹

Beginning in 1973, the FDA required the submission of data to establish the safety of antibiotic use in animals for nontherapeutic purposes (growth promotion and disease prevention). Required submissions include studies demonstrating that the antibiotic feed additive does not promote resistance to antibiotics used in human medicine or increase *Salmonella* shedding in fecal matter when used in animal feed for growth promotion and disease prevention, as recommended by an FDA task force in 1972.

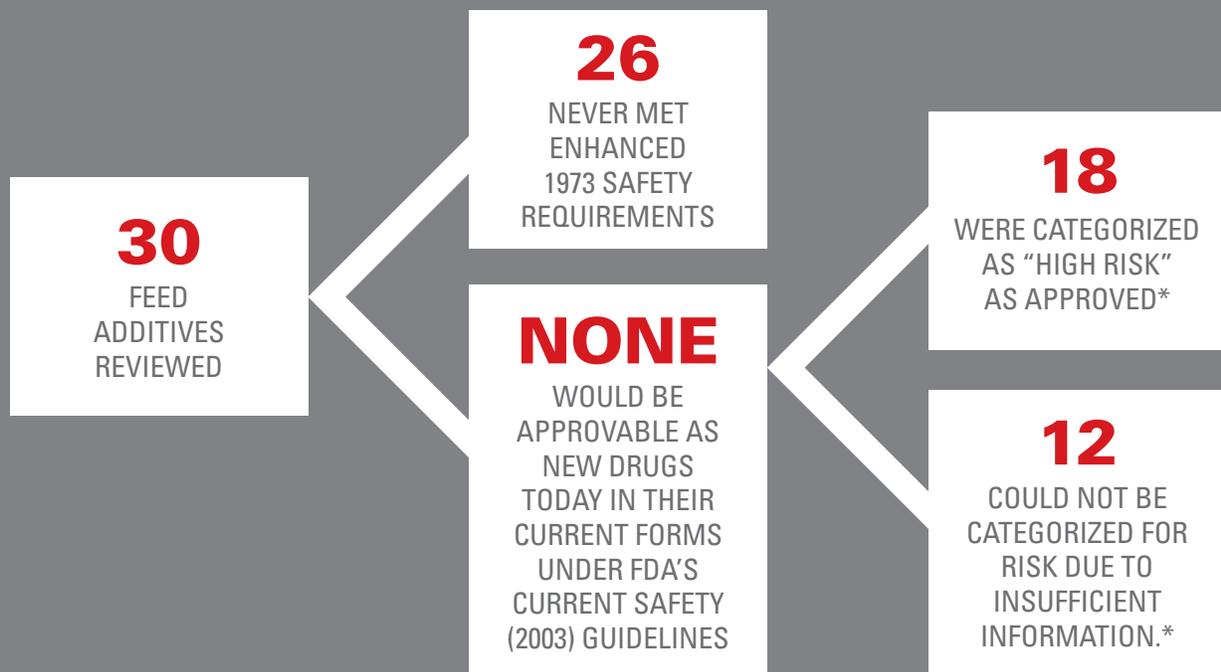
2003 Criteria (Guidance for Industry #152)⁶⁰

The FDA's 2003 Guidance criteria evaluate antibiotic use on the basis of three parameters:

1. Risk that the antibiotic(s) added to feed will result in the emergence or selection of resistant bacteria in the animal being fed.
2. Likelihood of human exposure to a foodborne bacterium of human health concern.
3. Risk of adverse human health consequences if exposure occurs. This focuses primarily on the importance of the antibiotic class for human medicine and whether its effectiveness might be compromised.

The three factors above are combined to create a risk estimation of high, medium, and low. The criteria then describe allowed conditions of use for each of the different levels of risk such as restrictions on number of animals that can be treated at a time.

FDA Review of Approved Nontherapeutic Antibiotic Animal Feed Additives



* FDA must not approve or must withdraw approval for drugs that are not shown to be safe. [Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360b(d)(1)(B), (e)(1)(B).]

Example of FDA Inaction: Antibiotic Feed Additives That Continue to Be Sold Without Being Shown to Be Safe

CASE 1: Pennchlor SP 250/500: An antibiotic feed additive that made it to market without demonstrating safety relating to antimicrobial resistance.

The sponsor proposed but never submitted studies to address the 1973 safety criteria.⁶¹ FDA's review does not mention any other studies that proved safety regarding the risk of antimicrobial resistance.⁶² FDA sent a letter to the sponsor in 2004 because it concluded that the feed additive likely posed a "high risk" for promoting resistance in bacteria of human health concern and requested additional safety information.⁶³ Notably, FDA's letter focused only on growth promotion claims for the feed additive, even though prevention claims were approved for exactly the same kind of use that FDA had found not to have met safety criteria in the growth promotion context.^{64,65,66} Both claims were approved with exactly the same restrictions (or lack thereof) on doses, dosage durations, and number of animals that can be treated.⁶⁷ There is nothing in the FDA documents that shows that the sponsor provided any new studies that addressed FDA's concerns.⁶⁸ FDA does not appear to have taken any action to withdraw approval even for the growth promotion claims it raised in its letter.⁶⁹ Today, Pennchlor SP250 continues to be marketed and is used in swine feeds.⁷⁰

CASE 2: Penicillin G Procaine 50/100: An antibiotic feed additive that failed to meet safety criteria and is still marketed today.

In 1997, the FDA asked the sponsor to voluntarily withdraw this antibiotic additive due to increased concern from public officials and members of the health care community regarding the emergence of antimicrobial resistance.⁷¹ In the same letter, the FDA stated that the product failed to meet antimicrobial-resistance safety criteria.⁷² In its review, FDA noted increased microbial resistance was observed when the antibiotic feed additive was administered in feed to animals.⁷³ The sponsor apparently disputed this finding⁷⁴, yet the FDA documents do not contain any other studies to address the safety issue.⁷⁵ FDA sent another letter to the sponsor in 2004 laying out its concerns about resistance.⁷⁶ The record does not show that the sponsor submitted any new studies.⁷⁷ FDA never required the sponsor to take the antibiotic feed additive off the market, and it is still sold as a growth promoter in feed.⁷⁸

Summary: Two medically important antibiotics in use in feed additives that have not been proven to be safe

Feed Additive name	Case I: Pennchlor SP 250/ Pennchlor SP 500	Case II: Penicillin G Procaine 50/100
NADA number	138-934	046-666
Antibiotic class in product	Penicillin, tetracycline, sulfonamides	Penicillin
Currently marketed by:	Pennfield Oil Co. ⁱ	Zoetis, Inc. ⁱⁱ
Approved for use in:	Swine	Non-laying chickens, turkeys, pheasants, and quail
Disease treatment and prevention:	Yes	No
Growth promotion:	Yes	Yes

i Pennfield Oil Co. is a large global animal health company. This company is not the original sponsoring company for the antibiotic feed additive.

ii Zoetis, a former business unit of Pfizer, is a large global animal health company. This company is not the original sponsoring company for the antibiotic feed additive.

HISTORY OF FDA INACTION

The failure to follow up on the recent review of antibiotic feed additives containing penicillin and/or tetracyclines is just the latest example of the FDA's inaction in the face of mounting evidence of public health threats stemming from the overuse and misuse of antibiotics in livestock. This inertia goes back four decades. In 1970, the FDA convened a task force of scientists from multiple agencies, including the National Institutes of Health, the U.S. Department of Agriculture, and the CDC, as well as from universities and industry. The task force found that the use of nontherapeutic antibiotics could threaten human health due to the likely rise of antibiotic resistance.⁷⁹

Similar findings in the Swann Report, a 1969 report issued by the British government that inspired the creation of the FDA task force, had spurred Europe into action, leading to the removal of penicillin and tetracycline as growth promoters in animal feed in several European countries.⁸⁰ The European Union has since banned the use of all antibiotic growth promoters in animal feed, and Denmark has gone further to disallow prophylactic uses.⁸¹

Following the findings of the FDA task force, FDA adopted the 1973 regulations requiring drug manufacturers to prove the safety of using antibiotics in animal feed.⁸² When drug manufacturers failed to establish safety pursuant to the 1973 regulations, in 1977, the FDA found that the use of penicillin and tetracyclines in animal feed was not shown to be safe and proposed to withdraw approval for those uses.⁸³ But the agency never followed through to complete the process. In 2012, NRDC sued to force the agency to act and won two court orders, including a directive to begin cancellation proceedings for penicillin and tetracyclines in animal feed.⁸⁴ The FDA then appealed. A decision is pending.

In 2003, the agency put out nonbinding guidelines (Guidance #152) that the agency follows in evaluating applications for new approvals of antibiotics for livestock use.⁸⁵ The 2003 guidelines were designed to increase the safety of new livestock drugs by reducing the likelihood that they would contribute to the development and spread of antibiotic-resistant bacteria via food. However, the 2003 guidelines do not apply to drugs that were previously approved, i.e., most of the antibiotics being used in livestock today.⁸⁶

Since then, the agency has recently approved more voluntary guidelines (Guidance #213)—non-binding recommendations—to guide the use and marketing of previously approved livestock antibiotics.⁸⁷ A critical loophole is that while FDA's proposed guidelines would encourage drug manufacturers to discontinue selling drugs to speed up animal growth ("growth promotion"), it does not discourage the continuation of very similar or even identical uses as long as the intent is to prevent disease ("disease prevention"), even in cases where the animals are not sick and the use is driven by the anticipated effects of crowded and unsanitary

conditions often found on livestock facilities. According to the FDA, "disease prevention involves the administration of an antimicrobial drug to animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered."⁸⁸ Because many drugs are approved for both growth promotion and disease prevention uses,⁸⁹ most current uses can continue under a different label.

Action to Protect Public Health

The FDA should immediately move to end nontherapeutic uses of the reviewed penicillins and tetracyclines and should limit uses of these medicines to treat sick animals or, in rare cases, to control disease outbreaks. The drug manufacturers of these antibiotic feed additives have failed for four decades to prove that they are safe for human health, as they were required to by law.⁹⁰ And FDA has failed to withdraw approval for these drugs in that time, in spite of the drug manufacturers' failure to prove the safety of their products.

As described above, the public health risks found by the FDA's review of 30 antibiotic feed additives are an indicator of a larger threat. The nontherapeutic livestock use of other penicillins and tetracyclines—and, indeed, any other medically important antibiotics—poses a risk of breeding resistant bacteria and contributing to the spread of antibiotic resistance. The FDA should therefore move swiftly to take the necessary steps to eliminate all nontherapeutic uses of all classes of medically important antibiotics in livestock production. FDA should also require improved reporting on livestock antibiotics, including reporting by users of these antibiotics, to enable the agency to track progress in meeting this goal.

Congress must act

If the FDA fails to take action, then Congress should step in to ensure that these essential medicines continue to be effective for humans for as long as possible. It should pass the Preventing Antibiotic Resistance Act and the Preservation of Antibiotics for Medical Treatment Act, both of which would phase out the nontherapeutic use of medically important antibiotics in animal feed.

Food companies and consumers should not wait for federal policy reform

While federal policymakers continue to delay, consumers and business leaders can make progress in promoting antibiotic stewardship in the livestock industry. Consumers should purchase animal products labeled "Certified Organic" or "No Antibiotics Administered" when they can. Food companies with large purchasing power should specify antibiotic stewardship requirements for producers who supply them. While many livestock producers have innovative production systems that are not reliant on nontherapeutic antibiotic use, others must now acknowledge the risks of these practices and transition their operations away from antibiotic dependency.

METHODS

EVALUATION OF DOCUMENTS:

Four volumes of the FDA review were received and the volumes included short and long versions of product reviews of penicillin and tetracycline feed additives. The FDA review was carried out from 2001 to 2010 by the Microbial Food Safety Team (HFV 157) in the Office of New Animal Drug Evaluation. Each review (Microbiologist's review) included a brief summary, a review of the administrative record, and conclusions. Specifically, a review of the administrative record included assessment of 21 C.F.R. § 558.15 (1973 safety and efficacy criteria) information, and assessment of the administrative record using Guidance for the Industry (GFI) #152. Extra documentation was provided that pertained to studies addressing 21 CFR 558.15, email correspondence related to the review team, correspondence between the sponsor and the Center for Veterinary Medicine (CVM), as well as background literature and related presentations or posters. Information presented in Appendix I is based on the short and long versions of the product reviews by the Microbial Food Safety Team including summarized 21 CFR 558.15 information, summarized correspondence and conclusions made by the FDA review team.

EVIDENCE OF MARKETING:

NADA numbers were entered into the Animal Drugs @ FDA (database of Approved Animal Drug Products, <http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/>). The current sponsor was identified and a search was performed for any evidence of current marketing (including product inserts, MSDS sheets, summary information, etc.) In addition, a search was performed using either the NADA number or the proprietary name and evidence of inclusion in any current or recent catalogs was included as evidence. In one case evidence was found of a generic product based on an identified NADA in the FDA review. The Feed Additive Compendium contained names of several products listed in Appendix I. Because NADA numbers are not associated with those products in the Compendium and many products have similar names, results from the Feed Additive Compendium are not included in Appendix II.

EVIDENCE OF WITHDRAWAL:

NADA numbers were entered into the Animal Drugs @ FDA (database of Approved Animal Drug Products, <http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/>). NADA numbers were cross referenced to the FDA Green Book (Section 6: Voluntary Withdrawals and monthly updates to Jan. 2014, The current status of the drug was assessed and in cases of withdrawal by the sponsor, such a status was noted.

APPENDIX I

Compilation of FDA scientists' review of 30 penicillin and tetracycline feed additives regarding 1973 criteria and Guidance #152.

Name of product	Volume of FDA Review	NADA Number	Met 1973 Safety Criteria	1973 Safety Criteria Citation	Risk Estimation (Guidance 152)	Risk Citation	Additional Information
Terramycin Animal Formula, Soluble Powder	Vol. I	008-622 ^{#ii}	Not met	FDA001732	High risk** ^{xi}	FDA001739	May not be applicable to 1973 criteria, Animal Drugs @FDA
Terramycin Type A medicated Articles	Vol. I	008-804	Met (in 1986)	FDA002102/ FDA002105/ FDA002110	Not enough information	FDA002114	
Aureomix Granular 500	Vol. II	035-688	Not met	See below	High risk**	FDA002145-002147	
(see above), Aureo S 700, Aureomycin	Vol. II	035-688, 035-805, 048-761	Not met	FDA002333	High risk**	FDA002325-002333	
Aureomix S 700 G	Vol. II	041-649	Not met	FDA003898	High risk	FDA003898	
Aureomix S 700 B	Vol. II	041-653	Not met	FDA003908-003910	Not enough information	FDA003910	
Penicillin 100/Penicillin G Procaine 50	Vol. II	046-666	Not met	FDA004026/FDA004029	High risk**	FDA004024-004027	
Penicillin G Procaine 50%	Vol. II	046-668	Not met	FDA004320-004322, FDA004324	High risk**	FDA004326-004330	
Chlormax products, Micro CTC 100	Vol. II	046-699	Not met	FDA004453-004454	High risk**	FDA004459	
Chlorachel 50, Pfi-chlor products	Vol. II	049-287	Not met	FDA0044486	High risk**	FDA004469-004476	
Rainbrook Broiler Premix No. 1	Vol. II	049-462	Not met	FDA004494	High risk**	FDA004491-004493	Withdrawn, Green book/Animal Drugs@FDA

APPENDIX I

Name of product	Volume of FDA Review	NADA Number	Met 1973 Safety Criteria	1973 Safety Criteria Citation	Risk Estimation (Guidance 152)	Risk Citation	Additional Information
Aureomycin Soluble Powder	Vol. II	055-020 [#]	Not met	FDA004521	Not enough information	FDA004522	May not be applicable to 1973 criteria, Animal Drugs @FDA
Penicillin G Potassium	Vol. II	055-060*	N/A	FDA004532	High risk	FDA004533-004536	1973 criteria not applicable FDA004533
Tetracycline Soluble Powder	Vol. III	065-496 [#]	Not met	FDA007239	High risk**	FDA004619-004623	May not be applicable to 1973 criteria, Animal Drugs @FDA
ChlorMax SP products, Chlorachel 250	Vol. III	091-668	Not met	FDA004730	High risk**	FDA004724-04730	
CLTC 100 MR, CLTC 70	Vol. III	092-287	Not met	FDA004766	Not enough information	FDA004774	
OXTC products, Terramycin products	Vol. III	095-143	Not met	FDA004811	Not enough information	FDA004811- FDA004812	
Pfichlor 100S Milk Replacer	Vol. III	100-901	Not met	FDA004818	High risk	FDA004819	
Terramycin Premix	Vol. III	103-758	Not met	FDA004838	Not enough information	FDA004839	Withdrawn, ³ Animal Drugs@FDA
Pennchlor SP 250/ Pennchlor SP 500	Vol. III	138-934	Not met	FDA004849-004850, FDA004872	High risk**	FDA004872- 004876	
Oxytetracycline products, Pennox products	Vol. III	138-938	Not met	FDA004898	Not enough information	FD004899- 4902	
CSP 250/CSP 500	Vol. III	039-077	Not met	FDA006977	High risk**	FDA006973- 006977	

APPENDIX I

Name of product	Volume of FDA Review	NADA Number	Met 1973 Safety Criteria	1973 Safety Criteria Citation	Risk Estimation (Guidance 152)	Risk Citation	Additional Information
Chloratet 100, Chloratet 90	Vol. III	048-480	Not met	FDA007160	High risk	FDA007160	
CLTC products	Vol. III	092-286	Not met	FDA007259	Not enough information	FDA007259	
Aureomix S 700-A, Aureomix S 700-D, Aureomix S 700-E, Aureomix S 700-F, Aureomix S 700-H	Vol. III	041-647 041-648 041-650 041-651 041-654	Not met	FDA007294	Not enough information	FDA007294	
Quratermaster Dry Cow Treatment	Vol. III	055-028*	N/A	FDA007729	High risk**	FDA007729-007738	1973 criteria not applicable (Vol. III FDA007723)
Aureomix S 700-C 2	Vol. IV	041-652	Not met	FDA009391	High Risk	FDA009391	

APPENDIX II

EVIDENCE OF MARKETING

1. Pennchlor SP 250 (NADA 138-934) – evidence of marketing through a feed company

“Pennchlor SP 250 – Product Description,” Feed Products and Company South, <http://www.feedproducts.net/products/pennchlor-SP-250.htm>, accessed November 25, 2013.

“Pennchlor SP-250- Specifications,” Feed Products and Company South, <http://www.feedproducts.net/documents/PennchlorSP250.pdf>, accessed November 24, 2013.

2. Aureomix 500 (NADA 035-688) – evidence of marketing through an animal pharmaceutical company

“Product inserts – Aureomix 500,” Zoetis, https://online.zoetis.com/US/EN/contact/product_information/Pages/ProductInserts.aspx, accessed November 25, 2013.

“Material Safety Data Sheet,” Zoetis, https://online.zoetis.com/US/EN/MSDS_PI/PI/Aureomix_500.pdf, accessed November 25, 2013.

3. Penicillin 100 (NADA 046-666) – evidence of marketing through an animal pharmaceutical company

“Product inserts – Penicillin 100,” Zoetis, https://online.zoetis.com/US/EN/contact/product_information/Pages/ProductInserts.aspx, accessed November 26, 2013.

“Material Safety Data Sheet,” Zoetis, https://online.zoetis.com/US/EN/MSDS_PI/PI/Penicillin_100.pdf, accessed November 25, 2013.

4. Chloratet (NADA 048-480) – evidence of marketing through a supplier company

“PALS feed additives and medication products catalog” PALS USA, <http://palsusa.com/files/PALSMedCatalog.pdf>, last accessed November 21, 2013.

5. Terramycin (NADA 008-622) – evidence of marketing of the generic (ANADA 200-026) based on this NADA by a supplier company

“Supplemental Abbreviated New Animal Drug Application” Food and Drug Administration, <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm061570.pdf>, last accessed on November 24, 2013.

“Terramycin 343-soluble powder” Revival Animal Health, <http://www.revivalanimal.com/Terramycin-343-Soluble-Powder-Generic.html>, last accessed on November 25, 2013.

6. Aureomycin NADA (48-761) – evidence of marketing by an animal pharmaceutical company

“Product insert - Aureomycin 50, 90, 100 Granular,” Zoetis, https://online.zoetis.com/US/EN/contact/product_information/Pages/ProductInserts.aspx, accessed November 25, 2013.

“Material Safety Data Sheet,” Zoetis, https://online.zoetis.com/US/EN/MSDS_PI/PI/Aureomycin_50_90_100_Granular-swine.pdf, accessed November 25, 2013.

7. Pennox 100MR (NADA 138-938) – Evidence of marketing by a supplier

“Pennox 100MR – Product Description,” Feed Products and Company South, <http://www.feedproducts.net/products/pennox-100-MR.htm>, accessed November 25, 2013.

“Pennox 100MR- Specifications,” Feed Products and Company South, last modified October 2010, <http://www.feedproducts.net/documents/Pennox100MR.pdf>, accessed November 24, 2013.

8. CLTC (NADA 92-287) – Evidence of marketing by a supplier and by inclusion in a USDA risk management program

“CLTC-100 MR” Animart Dairy and Livestock solutions, <http://www.animart.com/store/cltc-100-mr-50lb-drum/>, accessed November 24, 2013.

“CLTC 100MR” Food Animal Residue Avoidance Databank, <http://www.farad.org/vetgram/ProductInfo.asp?byNada=092-287>, accessed November 24, 2013.

9. Chlormax (NADA 46-669) – Evidence of marketing by an animal pharmaceutical company

“Product inserts – Chlormax,” Zoetis https://online.zoetis.com/US/EN/contact/product_information/Pages/ProductInserts.aspx, accessed November 25, 2013.

“Material Safety Data Sheet,” Zoetis, https://online.zoetis.com/US/EN/PublishingImages/Poultry%20Literature%20Library/US-EN/ChlorMax_Product_Profile_ZP130030_EN_Zoetis.pdf, accessed November 25, 2013.

Note: All products above are also listed by brand name in Feed Additive Compendium.

APPENDIX III

Selection of correspondence between Center for Veterinary Medicine and sponsors on FDA review conclusions.

NADA 046-666

Excerpt from letter sent to sponsor: "The administrative record does not contain sufficient information to alleviate the Center [for Veterinary Medicine]'s concern about the use of your product and its possible role in the emergence and dissemination of antimicrobial resistance."

Food and Drug Administration, Letter from FDA to Sponsor of NADA 046-666, May 26, 2004, Vol. III: FDA007516.

Excerpt from sponsor response: "[W]e wish to advise CVM of our strongly held view that these products, with the current claims, remain safe and effective.... The amendment to the FY 2001 appropriation directed a review of previous approvals. It did not alter the standards applicable to withdrawing approval to allow withdrawal based on nonscientifically based precautionary grounds. We believe the agency should be able to separate the justifiable concerns related to the development of antibiotic resistant human pathogens and discern that [the sponsor's] subtherapeutic penicillins are not the source of, or even a measurable contributor to, this public health issue."

Food and Drug Administration, Letter from Sponsor (of NADA 046-666, 035-688 039-077, and 091-668) to FDA, October 22, 2004, Vol. III: FDA008180-2.^{iv} Note: The sponsoring company sent the same letter as a response to FDA's letters regarding four separate NADAs.

NADA 046-668

Excerpt from letter sent to sponsor: "The administrative record does not contain sufficient information to alleviate the Center [for Veterinary Medicine]'s concern about the use of your product and its possible role in the emergence and dissemination of antimicrobial resistance."

Food and Drug Administration, Letter from FDA to Sponsor of NADA 046-668, received May 26, 2004, Vol. III: FDA007518.

Excerpt from the sponsor response: "[The sponsor] has been unable to make a decision on how to proceed on this issue. Although [Center for Veterinary Medicine] did supply us with a copy of the presentation given at the meeting, very little information was presented on the hazard characterization. In addition, it would be helpful for us to see a more complete description of the risk assessment so that we can determine what additional data may be collected/supplied to help support a more thorough evaluation."

Food and Drug Administration, Letter from Sponsor (of NADA 046-668) to FDA, November 15, 2004, Vol. III: FDA008950.

NADAs 035-688, 039-077, 091-668

Excerpt from letter sent to sponsor: "The administrative record does not contain sufficient information to alleviate the Center [for Veterinary Medicine]'s concern about the use of your product and its possible role in the emergence and dissemination of antimicrobial resistance."

Food and Drug Administration, Letter from FDA to Sponsor of NADA 035-688, 039-077, and 091-668, May 26, 2004, Vol. III: FDA007522.

Excerpt from sponsor response: "... We wish to advise CVM of our strongly held view that these products, with the current claims, remain safe and effective... The amendment to the FY 2001 appropriation directed a review of previous approvals. It did not alter the standards applicable to withdrawing approval to allow withdrawal based on nonscientifically based precautionary grounds. We believe the agency should be able to separate the justifiable concerns related to the development of antibiotic resistant human pathogens and discern that [the sponsor's] subtherapeutic penicillins are not the source of, or even a measurable contributor to, this public health issue."

Food and Drug Administration, Letter from Sponsor (of NADA 046-666, 035-688 039-077, and 091-668) to FDA, October 22, 2004, Vol. III: FDA008180-2.^{iv}

NADA 138-934

Excerpt from letter sent to sponsor: "The administrative record does not contain sufficient information to alleviate the Center [for Veterinary Medicine]'s concern about the use of your product and its possible role in the emergence and dissemination of antimicrobial resistance."

Food and Drug Administration, Letter from FDA to Sponsor of NADA 138-934, May 26, 2004, Vol. III: FDA007526.

Excerpt of FDA's summary of the sponsor's response: "The firm submitted a letter dated July 31, 2006 stating that they would remove the 'growth promotion and increased feed efficiency' indication from their label, as long as the other firms with the same product and indication did so as well...The firms also submitted (January 4, 2005) the results of a literature search... Specific information to address the data gaps in the microbial food safety assessment was not retrieved by the search terms used by the firm."

Food and Drug Administration, Microbial Food Safety Team (HFV-157), Brown Amendment Review of NADA 138-934, Vol. III: FDA004849-50

Endnotes

- 1 As noted, we use the term “nontherapeutic use” to refer to the use of antibiotics to speed up animal growth and prevent diseases. Antibiotics are typically administered for these purposes to large groups of animals for extended periods of time. We use “therapeutic” use to mean the use of antibiotics to treat sick animals or to control disease outbreaks in rare circumstances. FDA regulations refer to growth promotion and disease prevention uses as “subtherapeutic.” 21 C.F.R. § 558.15.
- 2 Penicillin-Containing Premixes Notice, 42 Fed. Reg. 43,772 (Aug. 30, 1977); Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes; Opportunity for Hearing, 42 Fed. Reg. 56,264 (Oct. 21, 1977)
- 3 Pew Charitable Trusts, “Record-High Antibiotics Sales for Meat and Poultry Production,” www.pewhealth.org/other-resource/record-high-antibiotic-sales-for-meat-and-poultry-production-85899449119, February 6, 2013, (accessed January 10, 2014); Food and Drug Administration, *2011 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM338170.pdf>. Note: We are reporting here the statistic for all classes of antibiotics used in human medicine, and we have excluded ionophores. The commonly reported 80 percent statistic includes ionophores.
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- 42 See, e.g., Food and Drug Administration, 2011 Retail Meat Report, National Antimicrobial Resistance Monitoring System, 27 tbl.10 n.2, <http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf>.
- 43 FDA did not respond to the FOIA request until NRDC filed a lawsuit; subsequently a settlement was reached and documents were made available.
- 44 *Natural Resources Defense Council v. United States Food and Drug Administration*, 884 F.Supp.2d 127, 131-32 (S.D.N.Y. 2012) (hereinafter "NRDC v. FDA").
- 45 FDA also reviewed two antibiotics products that were not approved for use in animal feed or water, and determined that they are "high risk" under the 2003 guidelines discussed further below. The antibiotic products are approved for intramammary application to dairy cows (NADA 055-028), and for treatment use (NADA 055-060). They were not required to meet the 1973 safety requirements, which focused on the safety of antibiotic feed additives. FDA examined the topical antibiotic because it was approved for preventive use, but it is not clear why FDA reviewed the antibiotic product approved for treatment. It remains unclear if and how safety for human health was established for these two antibiotic products; Food and Drug Administration, Microbiologist's Review of NADA 055-028, Vol. III, FDA007723-7739; Food and Drug Administration, Microbiologist's Review of NADA 055-060, Vol. II, FDA004531-4537.
- 46 See example of credentials listed in the individual reviews, Food and Drug Administration, Microbiologist's Review of NADA 008-622, Vol. III, FDA007076.
- 47 Senate and House Conference Committee on the amendment of the Senate to H.R. 2330, "Making appropriations for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies programs for the fiscal year ending September 30, 2002, and for other purposes," 107th Congress, 1st session, November 9, 2001, H.R. Rep. 107-275, at 82 (2001), www.gpo.gov/fdsys/pkg/CRPT-107hrpt275/pdf/CRPT-107hrpt275.pdf (accessed October 16, 2013); see, e.g., Letter from FDA to Sponsor of NADA 046-666, May 26, 2004, Vol. III: FDA007515.
- 48 Food and Drug Administration, Microbiologist's Review of NADA 065-123, Tetracycline Soluble Powder, Vol. III, FDA004566-67.
- 49 Appendix I, Column 4, shows which antibiotics failed to meet the 1973 criteria.
- 50 NRDC v. FDA, 884 F.Supp.2d at 133.
- 51 Three antibiotic products (NADA 065-496, 055-020, and 008-622) are additives approved for administration to animals for fewer than 14 days and the 1973 criteria may not apply. "In the past, FDA has referred to 'subtherapeutic' uses at various times to include: (1) 'increased rate of gain, disease prevention, etc.' (Ref. 7); (2) 'any use of an antibacterial drug continuously in feed for longer than 14 days' (Ref. 23); and (3) 'lower levels than therapeutic levels needed to cure disease.' (Refs. 1 and 2)." Withdrawal of NOOH; Penicillin and Tetracycline Used in Animal Feed, 76 Fed. Reg. 79697, 79700 (Dec. 22, 2011). See Appendix I, Column 4 and 8, show which antibiotics failed to meet the 1973 criteria and if the 1973 criteria were applicable.
- 52 See Food and Drug Administration, Microbiologist's Review of NADA 008-804, Vol. I, FDA002097, FDA002114. The approved NADA covers several versions of the same feed additive, a Terramycin Animal Mix.
- 53 See Appendix I, column 5.
- 54 Food and Drug Administration, Guidance for Industry No. 152, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*, 2003, at 23-25 www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf.
- 55 Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360b(d)(1)(B).
- 56 *Id.*, § 360b(e)(1)(B).
- 57 See pages following documents cited in Appendix III.
- 58 See Food and Drug Administration, Approved Animal Drug Products Online (Green Book), <http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm> (last accessed January 15, 2014). The two drugs that were voluntarily discontinued or withdrawn are Rainbrook Broiler Premix No. 1 (NADA No. 49-462) and Terramycin Premix (NADA No. 103-758). Food and Drug Administration, Microbiology Food Safety Review of NADA 49-462, at 6-7, Vol. II, FDA004486-87; Food and Drug Administration, Microbial Food Safety Review of NADA 103-758, at 1-2, Vol. III, FDA004838-39. Please note that the FDA database at AnimalDrugs@FDA (<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>) lists NADA 103-758 as voluntarily withdrawn; however, the official "Green Book" does not.
- 59 NRDC v. FDA, 884 F.Supp.2d at 133 (citing 42 Fed.Reg. 43,772, 43,774 (Aug. 30, 1977)).
- 60 Food and Drug Administration, Guidance for Industry No. 152, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*, 2003, www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf (accessed October 10, 2013) (hereinafter, "Guidance #152").
- 61 Food and Drug Administration, Microbiologist's Review of NADA 134-938 "Part I: Summary of Findings," Vol. III, FDA004872. ii. *Id.*
- 62 *Id.*
- 63 See Appendix III, NADA 138-934, Excerpt from FDA letter sent to sponsor.
- 64 See Approved usages for NADA 134-938, Vol. III, FDA004847-48; 21 C.F.R. § 558.145.
- 65 See Food and Drug Administration, Microbiologist's Review of NADA 134-938, at 24-25, Vol. III, FDA004876-77.
- 66 FDA's current statements on the issue of preventive claims, in non-binding policy documents such as Guidance #213, explain that FDA does not consider prevention uses to be subtherapeutic anymore, contradicting its own binding regulations, 21 C.F.R. § 558.15, despite the fact that the claims may overlap in the use allowed.
- 67 See Approved usages for NADA 134-938, Vol. III, FDA004847-48; 21 C.F.R. § 558.145.
- 68 See Appendix III, NADA 138-934, Excerpt from FDA's summary of the sponsor's response; see also Food and Drug Administration documents concerning NADA 134-938, Vol. III, FDA004846-4885.
- 69 See Food and Drug Administration documents concerning NADA 134-938, Vol. III, FDA004846-4885.
- 70 See Appendix II.

71 “From CVM to the sponsor... The letter indicates that considerable concern is being expressed by public health officials and representatives of the human health care community regarding the emergence of antimicrobial resistance. Attention is being drawn to the use of antimicrobials in animals as a source of the increasing resistance... The sponsor is asked to voluntarily withdraw their product.” Food and Drug Administration, Microbiologist’s Review of NADA 046-666, Part I: Review of Administrative Record, Vol. II, FDA003974.

72 “From CVM to the sponsor... The letter also states that the products subject to this NADA were determined to be effective for increasing rate of growth and improving feed efficiency under the DESI review, the products failed to meet antimicrobial resistance criteria established under 21 CFR 558.15 and as a result...were proposed for withdrawal via an NOOH published in 1977.” Food and Drug Administration, Microbiologist’s Review of NADA 046-666, Part I: Review of Administrative Record, Vol. II, FDA003974.

73 “It is interesting to note that although the sponsor makes the following statement in the body of their report, ‘Among the non-infected groups, there were significantly more ampicillin, chloramphenicol, nitrofurantoin and kanamycin resistant *E. coli* in the treated group than in the control group,’ this does not appear in the conclusions section of their report.” Food and Drug Administration, Microbiologist’s Review of NADA 046-666, Review of Data Pertaining to 558.15, Vol. II, FDA004019; see Letter from FDA to Sponsor of NADA 046-666, May 26, 2004, Vol. III, FDA007515 (noting that CVM concluded that “there were still questions about the observed increases in resistant *Salmonella* and *E. coli*”).

74 “From sponsor: ‘We are of course, aware of the renewed controversy over the use of certain antibacterials in animals; however, we continue to believe that when their safety is called into question, new animal drug approvals should only be withdrawn when there is sound scientific evidence for so doing. Mere speculation and theory should not be a basis for withdrawal of approval.’” Food and Drug Administration, Microbiologist’s Review of NADA 046-666, Part I: Review of Administrative Record, Vol. II, FDA003974.

75 See Food and Drug Administration documents concerning NADA 046-666, Vol. II, FDA003946-4075.

76 See Appendix III, NADA 046-666, Excerpt from FDA letter sent to sponsor.

77 *Id.*

78 “Product inserts – Penicillin 100,” Zoetis, last modified 2013, https://online.zoetis.com/US/EN/contact/product_information/Pages/ProductInserts.aspx, accessed November 26, 2013; “Material Safety Data Sheet,” Zoetis, https://online.zoetis.com/US/EN/MSDS_PI/PI/Penicillin_100.pdf, accessed November 25, 2013; “PALS feed additives and medication products catalog” PALS USA, <http://palsusa.com/files/PALSMedCatalog.pdf>, last accessed November 21, 2013.

79 *NRDC v. FDA*, 884 F.Supp.2d at 132-33.

80 Carol Cogliani, Herman Goossens, and Christina Greko, *Restricting Antimicrobial Use in Food Animals: Lessons from Europe*, *Microbe Magazine* (June 2011), www.microbemagazine.org/index.php?option=com_content&view=article&id=3458:restricting-antimicrobial-use-in-food-animals-lessons-from-europe&catid=752&Itemid=995.

81 Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture: Hearing Before the House Committee on Energy and Commerce, Subcommittee on Health, 111th Congress, (July 14, 2010) (statement of Per Henriksen, D.V.M., Ph.D., Head, Division for Chemical Food Safety, Animal Welfare, and Veterinary Medicinal Products, Danish Veterinary and Food Administration), <http://democrats.energycommerce.house.gov/sites/default/files/documents/Testimony-Henriksen-HE-Antibiotic-Resistance-Animal-Agriculture-2010-7-14.pdf>.

82 *NRDC v. FDA*, 884 F.Supp.2d at 133.

83 *Id.* at 133-34.

84 *Id. generally*; *Natural Resources Defense Council v. U.S. Food and Drug Administration*, 872 F.Supp.2d 318 (S.D.N.Y. 2012).

85 Guidance #152.

86 Government Accountability Office, Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals 24 (September 2011), <http://www.gao.gov/assets/330/323090.pdf>; Food and Drug Administration, Guidance for Industry No. 152, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* (October 23, 2003), www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf.

87 Food and Drug Administration, Guidance for Industry No. 213, *New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209 (December 2013)*, <http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm299624.pdf> (hereinafter, “Guidance #213”).

88 Food and Drug Administration, Guidance for Industry No. 209, *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals* 21 n.5 (April 13 2012), <http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf>.

89 Government Accountability Office, Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals 28 (September 2011), <http://www.gao.gov/assets/330/323090.pdf>.

90 21 C.F.R. § 558.15.

Method and Appendices endnotes

i For all of the antibiotic feed additives listed in this appendix, FDA did not have sufficient data to conduct a thorough risk assessment. However, for 18 antibiotic feed additives, it had sufficient information to carry out an abbreviated risk assessment. Even for these 18 additives, the assessment was more thorough for some additives than for others. “High risk” indicates that FDA scientists conducted a basic risk assessment. “High risk**” indicates that FDA conducted a more detailed assessment considering release, exposure, and consequence. See the following for example: Food and Drug Administration, Assessment of the Administrative Record using Guidance for Industry #152 – NADA 091-668, Vol. III, FDA004724-4730. For the other 12 additives, FDA concluded that it simply did not have sufficient information to be able to make any determination about risk. These additives are thus not shown to be safe.

ii *Two antibiotic products (NADA 055-060 and NADA 055-028) are not included in the 30 antibiotic feed additives discussed in the main text. #Three antibiotic products (NADA 065-496, 055-020, and 008-622) are additives approved for administration to animals for fewer than 14 days as indicated in Animal Drugs @ FDA database and the 1973 criteria may not be applicable.. (See main text for further information). Animal Drugs @ FDA database, <http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>

iii Please note that the FDA database at AnimalDrugs@FDA (<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>) lists NADA 103-758 as voluntarily withdrawn; however, the official “Green Book” does not.

iv Note that the same sponsor is associated with NADAs 046-666, 035-688, 039-077, and 091-668. The sponsor sent only one letter in response to FDA’s concerns and comments on all four NADAs.



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